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WITNESS my hand this
Eighteenth day of August 2003

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Regulation 3.2

Melbourne Health

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Diagnostic and therapeutic agents"

The invention is described in the following statement:

DIAGNOSTIC AND THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention relates generally to diagnostic and therapeutic agents. More particularly, the present invention provides mammalian transcription factors which function in the modulation of expression of genetic sequences. The present invention further provides nucleic acid molecules encoding the transcription factors as well as nucleic acid and/or proteinaceous molecules with which the transcription factors interact. The transcription factors of the present invention or molecules interacting with same may be used *inter alia* in the generation of a range of diagnostic and therapeutic agents for a range of conditions.

BACKGROUND OF THE INVENTION

Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in any country.

Bibliographic details of references provided in the subject specification are listed at the end of the specification.

The increasing sophistication of recombinant DNA techniques has provided significant progress in understanding the mechanisms involved in regulating eukaryotic gene expression. This is greatly facilitating research and development in the plant, agricultural, medical and veterinary industries. Transcription factors are an important component in the control of gene expression. However, despite their importance, mammalian transcription factors have not been well investigated for their diagnostic and therapeutic potential.

RNA polymerases in eukaryotic cells cannot initiate transcription alone; before transcription can begin, they require interaction between transcription factors and the

promoter. These factors assemble at the promoter and, *via* a series of steps, facilitate both the binding of RNA polymerase II to the promoter and its subsequent phosphorylation and release to initiate transcription.

In addition to these general transcription factors, many thousands of transcription activators and/or negative regulators (inhibitors) exist, which control the process of initiation of gene transcription from great distances along the DNA. These factors influence the timing and extent of transcription of a particular gene. Indeed, they control whether and to what extent a particular gene is transcribed in a cell of a particular tissue type. Although most gene regulators identified to date have been found to be proteins, some transcription factors may also be RNA molecules.

In *Drosophila*, the transcription factor known as "Grainyhead" regulates key developmental process in the embryo and is encoded by the gene *grainyhead*. During development, Grainyhead is initially involved in dorsal/ventral and terminal patterning of the newly fertilized embryo through the formation of multi-protein complexes that repress transcription from the *decapentaplegic*, *tailless* and *zerknuellt* genes (Huang *et al.*, *Genes Dev. 9:* 3177-3189, 1995; Liaw *et al.*, *Genes Dev. 9:* 3163-3176, 1995). Later, *grainyhead* is predominantly expressed in the embryonic central nervous system in cuticle-producing tissues, where it binds to promoters and influences transcription from other developmentally regulated genes including *engrailed*, *fushi tarazu* and *Ultrabithorax* (Bray *et al.*, *Genes Dev. 3:* 1130-1145, 1989; Dynlacht *et al.*, *Genes Dev. 3:* 1677-1688, 1989; Biggin and Tjian, *Cell 53:* 699-711, 1988; Soeller *et al.*, *Genes Dev. 2:* 68-81, 1988; Dynlacht *et al.*, *Cell 56:* 563-576, 1991; Attardi and Tjian, *Genes Dev. 7:* 1341-1353, 1993; Uv *et al.*, *Mol. Cell Biol. 14:* 4020-4031, 1994).

The importance of *grainyhead* in *Drosophila* development is emphasised by the embryonic lethal phenotype observed in flies carrying mutations in this gene. The embryos have flimsy cuticles, grainy and discontinuous head skeletons and patchy tracheal tubes (Bray and Kafatos, *Genes Dev. 5:* 1672-1683, 1991). A neuroblast-specific isoform of the protein, arising from alternate splicing, has also been identified. A mutation that abolishes

this isoform is pupal- and adult- lethal, and flies demonstrate uncoordinated movements (Uv *et al., Mol. Cell Biol. 17:* 6727-6735, 1997).

Mammalian homologs of *grainyhead* have previously been proposed, including three genes designated *CP2, LBP-1a* and *LBP-9*. Studies have implicated them in a wide variety of cellular and developmental events including T cell proliferation, globin gene expression and steroid biosynthesis (Sueyoshi *et al., Mol. Cell Biol. 15:* 4158-4166, 1995; Jane *et al., EMBO J. 14:* 97-105, 1995; Volker *et al., Genes Development 11:* 1435-1446, 1997; Zhou *et al., Mol. Cell Biol. 20:* 7662-7672, 2000). However, *in situ* analyses of both *CP2* and *LBP-1a* reveal ubiquitous expression of both genes, unlike the highly restricted pattern observed with *grainyhead* in *Drosophila* (Bray *et al.*, 1989, *supra*; Dynlacht *et al.*, 1989, *supra*; Bray and Kafatos, 1991, *supra*; Ramamurthy *et al., J. Biol. Chem. 276:* 7836-7842, 2001). It is concluded, therefore, that these genes are not close homologs of *grainyhead.*

There is a need to identify other mammalian transcription factors and in particular close mammalian homologs of Grainyhead and to use these to develop a range of diagnostic and therapeutic agents.

SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Nucleotide and amino acid sequences are referred to by a sequence identifier number (SEQ ID NO:). The SEQ ID NOs: correspond numerically to the sequence identifiers <400>1 (SEQ ID NO:1), <400>2 (SEQ ID NO:2), etc. A sequence listing is provided at the end of the specification. A summary of the SEQ ID NOs is provided in Table 1.

Genetic sequences were studied exhibited homology at the nucleotide and/or amino acid level to a *Drosophila* gene, the product of which is involved in body patterning where a fine balance between activation and inhibition of gene expression is critical to the correct development of cells and tissues into functional organisms. A large number of different families of transcription factors play a critical role in ensuring that this balance is maintained during embryological development. One such transcription factor, cloned from *Drosophila* and well-characterized, is Grainyhead (hereinafter referred to by its abbreviation, GRH). GRH is encoded by the gene *grainyhead* (*grh*). The inventors observed that the identity of previously published putative *grh* mammalian homologs showed much more ubiquitous expression compared with the highly restricted pattern exhibited by *Drosophila grh*. Furthermore, sequence similarity between the proposed mammalian homologs and the *Drosophila grh* sequence was relatively low. In accordance with the present invention, true *grh* homologs were identified and derived from mammalian tissue such as human and mouse tissue.

Accordingly, one aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a mammalian homolog of *Drosophila* GRH. A mammalian homolog of GRH is referred to herein as M-GRH. The corresponding gene is referred to as M-*grh*. A M-*grh* is

deemed a homolog of *Drosophila grh* (*D-grh*). If it comprises a nucleotide sequence having 60% or greater similarity to the nucleotide sequence of *D-grh* after optimal alignment. Likewise, a M-GRH is so defined if it comprises an amino acid sequence having 60% or greater similarity to the amino acid sequence of *Drosophila* GDH (*D-*GRH). There are four isoforms of *Drosophila grh* designated *D-grh* P1, *D-grh* P2, *D-grh* P3 and *D-grh* P4. The nucleotide sequence encoding *D-grh* is set forth in SEQ ID NO:17 and SEQ ID NO:34, SEQ ID NO:36 and SEQ ID NO:38, respectively. Mammalian sequences encompassed by the present invention include those derived from tissues of mouse and human including, for example, mouse embryo, human fetal brain and placenta, and mouse and human kidney. Reference herein to *Drosophila grp* includes any or all of its isoforms P1-P4.

The mammalian sequences identified by the present inventors show higher percentages of similarity to the *D-grh* sequence than the already identified mammalian sequences designated *CP2, LBP-1a* and *LBP-9*. In accordance with the present invention, it is proposed that the M-*grh* homologs disclosed are "true" *grh* homologs relative to *CP2, LBP-1a* and *LBP-9*. As a result of the analysis herein described, it is shown that the earlier sequences align phylogenetically with another distinct *Drosophila* factor, designated *Drosophila CP2*. A new family of transcription factors, highly conserved from *Drosophila* to human and having distinct tissue-specificity profiles, is now described in accordance with the present invention.

The true M-*grh* homologs of the present invention include mammalian *grainyhead* (gene: *mgr*; expression product: MGR), *brother of mgr* (gene: *bom*; expression product: BOM) and *sister of mgr* (gene *som*: protein: SOM). MGR has multiple isoforms including MGR p49 and MGR p70 in humans and MGR p61 in mice. A summary of the SEQ ID NOs for the M-*grh* and M-GRH molecules of the present invention are shown in Table 2. The sequences are provided in the Sequence Listing.

The present invention provides, therefore, expression products of the M-*grh* genes, *mgr, bom* and *som* as well as derivatives and homologs thereof. This aspect of the present

invention does not extend to *CP2, LBP-1a* or *LBP-9*.

Accordingly, another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a polypeptide comprising a predicted amino acid sequence substantially as set forth in SEQ ID NO:2 (human MGR p49), SEQ ID NO:4 (human MGR p70), SEQ ID NO:6 (human BOM), SEQ ID NO:8 (human SOM), SEQ ID NO:10 (murine MGR p49), SEQ ID NO:12 (murine MGR p70), SEQ ID NO:14 (murine BOM) or SEQ ID NO:16 (murine SOM) or an amino acid sequence having at least about 60% similarity to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16 after optimal alignment.

The preferred nucleic acid molecules comprise sequences of nucleotides substantially as set forth in SEQ ID NO:1 (human *mgr* p49), SEQ ID NO:3 (human *mgr* p70), SEQ ID NO:5 (human *bom*), SEQ ID NO:7 (human *som*), SEQ ID NO:9 (murine *mgr* p61), SEQ ID NO:11 (murine *mgr* p70), SEQ ID NO:13 (murine *bom*) or SEQ ID NO:15 (murine *som*) or complementary forms thereof, or a nucleotide sequence having at least about 60% similarity to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 after optimal alignment or their complementary forms or a nucleotide sequence capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or complementary forms thereof under low stringency conditions. Again, this aspect of the present invention does not extend to nucleic acid molecules encoding CP2, LBP-1 and LBP-9.

The present invention further extends to recombinant forms of the M-GRH molecules. Preferred recombinant M-GRH molecules having amino acid sequences defined in parenthesis include human MGR p49 (SEQ ID NO:2), human MGR p70 (SEQ ID NO:4), human BOM (SEQ ID NO:6), human SOM (SEQ ID NO:8), murine MGR p61 (SEQ ID NO:10), murine MGR p70 (SEQ ID NO:12), murine BOM (SEQ ID NO:14) and murine SOM (SEQ ID NO:16).

Reference to "M-GRH" molecules include derivatives, homologs and analogs thereof.

The mammalian transcription factors of the present invention are proposed to be involved in the regulation of expression of a range of genes such as but not limited to developmentally regulated genes involved in determining patterning. Some of the genes regulated encode critical products, the absence or malfunctioning of which, is proposed to lead to unwanted phenotypes and/or predispositions to certain medical conditions. That is, the presence of a mutation in and/or malfunction of a M-*grh* including over or under expression of the transcription factors of the present invention are proposed to cause incorrect regulation of one or more of these genes thereby leading to an inappropriate phenotype. The ability to detect mutations in the nucleotide sequences encoding the M-*grh* homologs permits the detection of a range of abnormalities or a predisposition for development of abnormalities. Furthermore, as many of the genes will be developmentally regulated genes, identification of the transcription factors permits identification of unknown developmentally regulated genes.

Accordingly, another aspect of the present invention contemplates a method for detecting a variation in a polynucleotide sequence encoding a M-GRH transcription factor.

Furthermore, the isolated nucleic acid molecules of the present invention may be able to be used to correct such an abnormality in a subject in need thereof or at risk of developing an abnormality. The nucleic acid molecules of the present invention may be comprised, therefore, within a suitable vector for delivery of all or part of the sequence to a recipient cell or tissue. The nucleic acid molecule or part thereof could also be administered directly for transient expression. The present invention provides, therefore, the potential for both a diagnostic and a therapeutic capability.

Accordingly, a further aspect of the present invention contemplates a genetic construct comprising a nucleotide sequence selected from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15 or a

nucleotide sequence having at least 60% similarity to one or more of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 after optimal alignment or a nucleotide sequence capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or a complementary form thereof under low stringency conditions.

In a related embodiment, the present invention provides a genetic construct comprising a promoter or functional equivalent thereof operably linked to a nucleotide sequence of the invention.

Genes are represented herein in lower case italics. Expression products (e.g. proteins or RNA) are represented in upper case, non-itallic letters. A summary of the genes and their expression products is provided in Table 1.

TABLE 1

Abbreviations

GENE	EXPRESSION PRODUCT
grainyhead (*grh*)	Grainyhead (GRH)
mammalian *grainyhead* homologs (M-*grh*)	mammalian grainyhead homologs (M-GRH)
mammalian *grainyhead* (*mgr*)	mammalian Grainyhead (MGR)
brother of mammalian *grainyhead* (*bom*)	brother of mammalian grainyhead (BOM)
sister of mammalian *grainyhead* (*som*)	sister of mammalian grainyhead (SOM)

A summary of sequence identifiers used throughout the specification is Table 2.

TABLE 2

Summary of sequence identifiers

SEQUENCE ID NO.	NAME	DESCRIPTION
1	human *mgr* p49	Nucleotide sequence encoding mammalian *grainyhead* derived from human fetal brain
2	human MGR p49	Predicted amino acid sequence corresponding to SEQ ID NO:1
3	human *mgr* p70	Nucleotide sequence encoding mammalian *grainyhead* being an isoform of SEQ ID NO:1, derived from human kidney
4	human MGR p70	Predicted amino acid sequence corresponding to SEQ ID NO:3
5	human *bom*	Nucleotide sequence encoding mammalian *grainyhead* derived from human placenta
6	human BOM	Predicted amino acid sequence corresponding to SEQ ID NO:5
7	human *som*	Nucleotide sequence encoding mammalian *grainyhead*
8	human SOM	Predicted amino acid sequence corresponding to SEQ ID NO:7
9	murine *mgr* p61	Nucleotide sequence encoding mammalian *grainyhead* derived from 17.5 day murine embryo
10	murine MGR p61	Predicted amino acid sequence corresponding to SEQ ID NO:9
11	murine *mgr* p70	Nucleotide sequence encoding mammalian *grainyhead* being an isoform of SEQ ID NO:9, derived from murine kidney
12	murine MGR p70	Predicted amino acid sequence corresponding to SEQ ID NO:11
13	murine *bom*	Nucleotide sequence encoding mammalian *grainyhead* derived from a murine embryonic carcinoma cell line (p19)
14	murine BOM	Predicted amino acid sequence corresponding to SEQ ID NO:13
15	murine *som*	Nucleotide sequence encoding mammalian *grainyhead*
16	murine SOM	Predicted amino acid sequence corresponding to SEQ ID NO:15
17	*grh*-P1	Nucleotide sequence encoding the *Drosophila*

SEQUENCE ID NO.	NAME	DESCRIPTION
		transcription factor designated *Grainyhead* (*grh*)
18	GRH-P1	Amino acid sequence corresponding to SEQ ID NO:18
19-20	human p49 *mgr*	primers
21-22	human p70 *mgr*	primers
23-24	human *bom*	primers
25-26	murine p70 *mgr*	primers
27-28	murine p61 *mgr*	primers
29-30	murine *bom*	primers
31-32	human S14	primers
33	*Drosophila dopa decarboxylase*	promoter
34	*Drosophila PCNA*	promoter
35	human Engrailed-1	promoter
36	*grh*-P2	Nucleotide sequence encoding the *Drosophila* transcription factor designated *Grainyhead* (*grh*) isoform P2
37	GRH-P2	Amino acid sequence corresponding to SEQ ID NO:36
38	*grh*-P3	Nucleotide sequence encoding the *Drosophila* transcription factor designated *Grainyhead* (*grh*) isoform P3
39	GRH-P3	Amino acid sequence corresponding to SEQ ID NO:38
40	*grh*-P4	Nucleotide sequence encoding the *Drosophila* transcription factor designated *Grainyhead* (*grh*) isoform P4
41	GRH-P4	Amino acid sequence corresponding to SEQ ID NO:40

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a representation showing that *mgr* genomic locus encodes two distinct isoforms. (A) Alignment of the predicted NH_2-terminal amino acid sequence of the p70 isoform of MGR and BOM. Amino acid identity is denoted by shared upper case letters and similarity by the (+) symbol. The first amino acids shared between p61 MGR and p70 MGR are given in bold. (B) Structure of the human and murine *mgr* genomic loci. Human genomic sequence was downloaded from the GenBank database (Accession Number AC010969) and aligned with cDNA sequences. Murine genomic clones were obtained from a 129 library and mapped by Southern analysis and PCR. Exons are denoted as E1-8 in human and E1-9 in murine. The two human MGR isoforms are denoted as p70 and p49 MGR and the two murine isoforms as p70 and p61 MGR. The scale of 1 kb is shown. (C) Identification of the murine p61 MGR promoter. Sequence was obtained from intron three from the MGR genomic locus and analyzed using the weight matrices of Bucher, *J. Mol. Biol. 212:* 563-578, 1990. The CAP site, TATA box and GC box are indicated. The cDNA start site is shown in arrows, the first ATG is given in bold and the splice site at the end of the first exon of p61 MGR is indicated.

Figure 2 is a photographic representation showing that p70 MGR binds to *Drosophila* gene regulatory sequences which bind *grh*. (A) p70 MGR binds to the *Drosophila PCNA* promoter. Nuclear extract from the JEG-3 cell line was studied in an EMSA with a *PCNA* promoter probe in the presence and absence of anti-MGR specific antisera. Antisera 611 was raised against peptides common to the p70 and p49 MGR proteins in the dimerization domain and antisera 67 was raised against unique peptides in the NH_2-terminal domain of p70 MGR. The migration of the MGR complex is shown in arrows. (B) p70 MGR binds to the *Drosophila dopo decarboxylase* promoter. Experimental conditions were as described for (A).

Figure 3 are representations showing that p70 MGR binds to and transactivates the human En-1 promoter. (A) Identification of a *grh* consensus DNA binding site in the human En-1 promoter. The consensus sequence for *grh* DNA binding compiled from an alignment of

the *Drosophila Ultrabithorax, Dopa decarboxylase* and *fushi tarazu* promoters was compared with the sequence of the proximal human En-1 promoter and the *Drosophila engrailed* promoter. The closed bracket indicates the extend of the *grainyhead* binding site in the *engrailed* promoter as defined by DNAseI footprinting. (B) Human p70 MGR binds to the human En-1 promoter. Nuclear extract from the JEG-3 cell line was studied in an EMSA with a *Ddc* promoter probe in the presence of pre-immune sera (lane 1), anti-MGR specific antisera 67 (detailed in legend to Figure 2) (lane 2) or cold competitor DNA (lanes 3-5). A 50-fold excess of the *Ddc* probe was used in lane 3 and a 10- and 20-fold excess of a human En-1 promoter probe in lanes 4 and 5, respectively. The migration of the MGR/DNA complex is shown by arrows. (C) Human p70 MGR transactivates the En-1 promoter. COS cells were transiently transfected with the proximal En-1 promoter containing the MGR binding site linked to a mimimal γ-globin promoter and a firefly luciferase reporter gene (solid columns), the miminal γ-globin promoter/luciferase reporter gene (open columns) and the TK promoter linked to the Renilla luciferase reporter gene (hatched columns) in the presence and absence of a p70 MGR expression vector (PCI-p70 MGR) as indicated. Transfection with the empty vector (pCI) served as the control. Luciferase levels were corrected for protein concentration and values were derived from two independent experiments performed in triplicate.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is predicated in part on the identification of mammalian homologs of the *Drosophila* transcription factor known as Grainyhead (GRH). GRH is encoded by the gene, *grainyhead* (*grh*) In *Drosophila*, mutations in this gene are associated with embryonic lethal phenotypes, indicating the importance of the gene for normal development and function. The mammalian homologs are proposed to be involved in the regulation of developmental and/or non-developmental genes. Identification and isolation of the mammalian homologs of *grh* (M-*grh*) enable the development of a range of diagnostic and therapeutic agents useful in the detection and treatment of genetic disorders.

The present invention provides, therefore, a family of mammalian-derived transcription factors, highly related from *Drosophila* to mammals. These transcription factors are more highly conserved than CP2, LBP-1a and LBP-9. The present invention does not extend to CP2, LBP-1 and LBP-9. Reference to a mammal in this context includes a human, livestock animal (e.g. sheep, cow, horse, pig, donkey, goat), laboratory test animal (e.g. mouse, rat, rabbit, guinea pig), companion animal (e.g. dog, cat) or captive wild animal. Most preferably, the animal is a human or murine species. Sources of the isolated nucleic acid molecules include a range of tissues, such as mouse embryo, human fetal brain and placenta, and mouse and human kidney. In view of the highly conserved nature of this family of M-*grh* nucleotide sequences, however, corresponding homologs from other tissues and from other mammalian species are intended to be included within the scope of the present invention. The term "homolog" as used herein, therefore, extends to encompass transcription factors from mammalian species encoded by nucleotide sequences which have substantial similarity to *Drosophilia grh* or a conserved region thereof. At the protein level, a homolog includes an amino acid sequence and/or tertiary structure having similarity to *Drosophila* GRH. In cases where the expression product of the M-*grh* is RNA, a homolog is defined by reference to the similar ribonucleotide sequence to that encoded by *Drosophila grh*.

M-ghd or M-GRH, i.e. a mammalian homolog of *Drosophila grh* or GRH is defined as

such by having a nucleotide or amino acid sequence which has 60% or greater similarity after optimal alignment to *Drosophila grh* or GRH.

Accordingly, one aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a mammalian homolog of *Drosophila grh*.

Reference to a mammalian homolog of *Drosophila* GRH (i.e. a M-GRH) preferably includes the mammalian homolog of grainyhead (MGR), brother of MGR (BOM) and sister of MGR (SOM). These transcription factors are encoded by *mgr*, *bom* and *som*, respectively. Reference to "MGR", "BOM" and "SOM" or *mgr*, *bom* and *som* includes all mutants, derivatives, homologs and analogs thereof. The present invention further extends, however, to all novel mammalian homologs of *Drosophila grh* but does not encompass CP2, LBP-1a or LBP-9. The nucleotide sequences for *Drosophila grh* are set forth in SEQ ID NO:17, SEQ ID NO:34, SEQ ID NO:36 and SEQ ID NO:38, respectively. Consequently, a mammalian homolog is defined herein as comprising a nucleotide sequence having at least about 60% sequence similarity to SEQ ID NO:17 or SEQ ID NO:34 or SEQ ID NO:36 or SEQ ID NO:38 after optimal alignment and/or being capable of hybridizing to SEQ ID NO:17 or SEQ ID NO:34 or SEQ ID NO:36 or SEQ ID NO:38 or its complementary form under low stringency conditions.

Accordingly, another aspect of the present invention provides an isolated nucleic acid molecule encoding a mammalian transcription factor or a functional part thereof comprising a sequence of nucleotides having at least 60% similarity to SEQ ID NO:17 or SEQ ID NO:34 or SEQ ID NO:36 or SEQ ID NO:38 after optimal alignment and/or being capable of hybridizing to SEQ ID NO:17 or its complementary form under low stringency conditions.

In a preferred embodiment, the isolated nucleic acid molecule encodes a proteinaceous form of a transcription factor. Examples of such mammalian protein transcription factors include human MGR p49 (SEQ ID NO:2), human MGR p70 (SEQ ID NO:4), human

BOM (SEQ ID NO:6), human SOM (SEQ ID NO:7), murine MGR p61 (SEQ ID NO:10), murine MGR p70 (SEQ ID NO:12), murine BOM (SEQ ID NO:14) and murine SOM (SEQ ID NO:16).

Accordingly, another aspect of the present invention is directed to an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a polypeptide having transcription factor activity and comprising an amino acid sequence substantially as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 or SEQ ID NO:16 or an amino acid sequence having at least about 60% similarity to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 or SEQ ID NO:16 after optimal alignment wherein said polypeptide is a mammalian homolog of *Drosophia* GRH.

Such a polypeptide is referred to herein as a M-GRH.

Preferred percentage amino acid similarity levels include at least about 61% or at least about 62% or at least about 63% or at least about 64% or at least about 65% or at least about 66% or at least about 67% or at least about 68% or at least about 69% or at least about 70% or at least about 71% or at least about 72% or at least about 73% or at least about 74% or at least about 75% or at least about 76% or at least about 77% or at least about 78% or at least about 79% or at least about 80% or at least about 81% or at least about 82% or at least about 83% or at least about 84% or at least about 85% or at least about 86% or at least about 87% or at least about 88% or at least about 89% or at least about 90% or at least about 91% or at least about 92% or at least about 93% or at least about 94% or at least about 95% or at least about 96% or at least about 97% or at least about 98% or at least about 99% similarity.

This aspect of the present invention includes derivatives of M-GRH molecules. Such derivatives include non-active fragments which encompass *inter alia* the binding domain as well as active isoforms.

A "derivative" of a polypeptide of the present invention also encompasses a portion or a part of a full-length parent polypeptide, which retains the transcription factor activity of the parent polypeptide. Such "biologically-active fragments" include deletion mutants and small peptides, for example, of at least 10, preferably at least 20 and more preferably at least 30 contiguous amino acids, which exhibit the requisite activity. Peptides of this type may be obtained through the application of standard recombinant nucleic acid techniques or synthesized using conventional liquid or solid phase synthesis techniques. For example, reference may be made to solution synthesis or solid phase synthesis as described, for example, in Chapter 9 entitled *"Peptide Synthesis"* by Atherton and Shephard which is included in a publication entitled *"Synthetic Vaccines"* edited by Nicholson and published by Blackwell Scientific Publications. Alternatively, peptides can be produced by digestion of an amino acid sequence of the invention with proteinases such as endoLys-C, endoArg-C, endoGlu-C and staphylococcus V8-protease. The digested fragments can be purified by, for example, high performance liquid chromatographic (HPLC) techniques. Any such fragment, irrespective of its means of generation, is to be understood as being encompassed by the term "derivative" as used herein.

In another embodiment, the present invention provides an isolated nucleic acid molecule encoding a mammalian transcription factor homolog of *Drosophila grh* (i.e. a M-GRH) and comprising a nucleotide sequence selected from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 and SEQ ID NO:15 or a nucleotide sequence having at least about 60% similarity to any one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 after optimal alignment or a nucleotide sequence capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or a complementary form thereof under low stringency conditions.

Preferably, percentage nucleotide similarity levels include at least about 61% 61% or at least about 62% or at least about 63% or at least about 64% or at least about 65% or at least about 66% or at least about 67% or at least about 68% or at least about 69% or at

least about 70% or at least about 71% or at least about 72% or at least about 73% or at least about 74% or at least about 75% or at least about 76% or at least about 77% or at least about 78% or at least about 79% or at least about 80% or at least about 81% or at least about 82% or at least about 83% or at least about 84% or at least about 85% or at least about 86% or at least about 87% or at least about 88% or at least about 89% or at least about 90% or at least about 91% or at least about 92% or at least about 93% or at least about 94% or at least about 95% or at least about 96% or at least about 97% or at least about 98% or at least about 99% similarity.

The term "similarity" as used herein includes exact identity between compared sequences at the nucleotide or amino acid level. Where there is non-identity at the nucleotide level, "similarity" includes differences between sequences which result in different amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. Where there is non-identity at the amino acid level, "similarity" includes amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. In a particularly preferred embodiment, nucleotide and sequence comparisons are made at the level of identity rather than similarity.

Terms used to describe sequence relationships between two or more polynucleotides or polypeptides include "reference sequence", "comparison window", "sequence similarity", "sequence identity", "percentage of sequence similarity", "percentage of sequence identity", "substantially similar" and "substantial identity". A "reference sequence" is at least 12 but frequently 15 to 18 and often at least 25 or above, such as 30 monomer units, inclusive of nucleotides and amino acid residues, in length. Because two polynucleotides may each comprise (1) a sequence (i.e. only a portion of the complete polynucleotide sequence) that is similar between the two polynucleotides, and (2) a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of sequence similarity. A "comparison window" refers to a conceptual segment of typically

12 contiguous residues that is compared to a reference sequence. The comparison window may comprise additions or deletions (i.e. gaps) of about 20% or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by computerized implementations of algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Drive Madison, WI, USA) or by inspection and the best alignment (i.e. resulting in the highest percentage homology over the comparison window) generated by any of the various methods selected. Reference also may be made to the BLAST family of programs as for example disclosed by Altschul *et al.* (*Nucl. Acids. Res. 25:* 3389, 1997). A detailed discussion of sequence analysis can be found in Unit 19.3 of Ausubel *et al.* (In: Current Protocols in Molecular Biology, John Wiley & Sons Inc. 1994-1998).

The terms "sequence similarity" and "sequence identity" as used herein refers to the extent that sequences are identical or functionally or structurally similar on a nucleotide-by-nucleotide basis or an amino acid-by-amino acid basis over a window of comparison. Thus, a "percentage of sequence identity", for example, is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g. A, T, C, G, I) or the identical amino acid residue (e.g. Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys and Met) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. For the purposes of the present invention, "sequence identity" will be understood to mean the "match percentage" calculated by the DNASIS computer program (Version 2.5 for windows; available from Hitachi Software engineering Co., Ltd., South San Francisco, California, USA) using standard defaults as used in the reference manual accompanying the software. Similar comments apply in relation to sequence similarity.

The present invention provides, therefore, an isolated nucleic acid molecule comprising a

sequence of nucleotides selected from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 and SEQ ID NO:15 or a complementary form thereof. Such nucleic acid molecules encode mammalian homologs of *Drosophila grh*. These mammalian homologs are proposed herein to be transcription factors.

The present invention extends to variants of the nucleic acid molecules. A variant is a molecule having less than 100% sequence identity to a M-*grh*. Generally, a variant will still hybridize to a M-*grh* sequence under low stringency conditions.

The term "variant" refers, therefore, to nucleotide sequences displaying substantial sequence identity with a reference nucleotide sequences or polynucleotides that hybridize with a reference sequence under stringency conditions that are defined hereinafter. The terms "nucleotide sequence", "polynucleotide" and "nucleic acid molecule" may be used herein interchangeably and encompass polynucleotides in which one or more nucleotides have been added or deleted, or replaced with different nucleotides. In this regard, it is well understood in the art that certain alterations inclusive of mutations, additions, deletions and substitutions can be made to a reference nucleotide sequence whereby the altered polynucleotide retains the biological function or activity of the reference polynucleotide. The term "variant" also includes naturally-occurring allelic variants.

Reference herein to a low stringency includes and encompasses from at least about 0 to at least about 15% v/v formamide and from at least about 1 M to at least about 2 M salt for hybridization, and at least about 1 M to at least about 2 M salt for washing conditions. Generally, low stringency is at from about 25-30°C to about 42°C. The temperature may be altered and higher temperatures used to replace formamide and/or to give alternative stringency conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5 M to at least about 0.9 M salt for hybridization, and at least about 0.5 M to at least about 0.9 M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31%

v/v to at least about 50% v/v formamide and from at least about 0.01 M to at least about 0.15 M salt for hybridization, and at least about 0.01 M to at least about 0.15 M salt for washing conditions. In general, washing is carried out $T_m = 69.3 + 0.41$ (G+C)% (Marmur and Doty, *J. Mol. Biol. 5:* 109, 1962). However, the T_m of a duplex DNA decreases by 1°C with every increase of 1% in the number of mismatch base pairs (Bonner and Laskey, *Eur. J. Biochem. 46:* 83, 1974). Formamide is optional in these hybridization conditions. Accordingly, particularly preferred levels of stringency are defined as follows: low stringency is 6 x SSC buffer, 0.1% w/v SDS at 25°-42°C; a moderate stringency is 2 x SSC buffer, 0.1% w/v SDS at a temperature in the range 20°C to 65°C; high stringency is 0.1 x SSC buffer, 0.1% w/v SDS at a temperature of at least 65°C.

The present invention extends to recombinant forms of the M-*grh* molecules as well as derivatives and homologs thereof.

Accordingly, another aspect of the present invention provides an isolated polypeptide having transcription factor activity, said polypeptide comprising a sequence of amino acids encoded by a nucleotide sequence selected from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or a nucleotide sequence having at least about 60% similarity to any one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or a nucleotide sequence capable of hybridizing to any one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or a complementary form thereof under low stringency conditions.

In a preferred embodiment, the present invention provides a recombinant M-*grh* comprising an amino acid sequence selected from SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 or SEQ ID NO:16 or an amino acid sequence having at least about 60% similarity to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 or SEQ ID NO:16.

This aspect of the present invention extends to derivatives, homologs and analogs of M-GRH molecules.

A "derivative" includes a mutant, fragment, part, portion or hybrid molecule. A derivative generally but not exclusively carries a single or multiple amino acid substitution, addition and/or deletion.

A "homolog" includes an analogous polypeptide having at least about 60% similar amino acid sequence from another animal species or from a different locus within the same species.

An "analog" is generally a chemical analog. Chemical analogs of the subject polypeptide contemplated herein include, but are not limited to, modification to side chains, incorporation of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogs.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with $NaBH_4$.

The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivitization, for example, to a corresponding amide.

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acid, contemplated herein is shown in Table 3.

TABLE 3

Non-conventional amino acid	Code	Non-conventional amino acid	Code
α-aminobutyric acid	Abu	L-N-methylalanine	Nmala
α-amino-α-methylbutyrate	Mgabu	L-N-methylarginine	Nmarg
aminocyclopropane-	Cpro	L-N-methylasparagine	Nmasn
carboxylate		L-N-methylaspartic acid	Nmasp
aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbornyl-	Norb	L-N-methylglutamine	Nmgln
carboxylate		L-N-methylglutamic acid	Nmglu
cyclohexylalanine	Chexa	L-Nmethylhistidine	Nmhis
cyclopentylalanine	Cpen	L-N-methylisolleucine	Nmile
D-alanine	Dal	L-N-methylleucine	Nmleu
D-arginine	Darg	L-N-methyllysine	Nmlys
D-aspartic acid	Dasp	L-N-methylmethionine	Nmmet
D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
D-isoleucine	Dile	L-N-methylproline	Nmpro
D-leucine	Dleu	L-N-methylserine	Nmser
D-lysine	Dlys	L-N-methylthreonine	Nmthr
D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
D-phenylalanine	Dphe	L-N-methylvaline	Nmval
D-proline	Dpro	L-N-methylethylglycine	Nmetg
D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
D-threonine	Dthr	L-norleucine	Nle

	D-tryptophan	Dtrp	L-norvaline	Nva
	D-tyrosine	Dtyr	α-methyl-aminoisobutyrate	Maib
	D-valine	Dval	α-methyl-γ-aminobutyrate	Mgabu
	D-α-methylalanine	Dmala	α-methylcyclohexylalanine	Mchexa
5	D-α-methylarginine	Dmarg	α-methylcylcopentylalanine	Mcpen
	D-α-methylasparagine	Dmasn	α-methyl-α-napthylalanine	Manap
	D-α-methylaspartate	Dmasp	α-methylpenicillamine	Mpen
	D-α-methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
	D-α-methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
10	D-α-methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
	D-α-methylisoleucine	Dmile	N-amino-α-methylbutyrate	Nmaabu
	D-α-methylleucine	Dmleu	α-napthylalanine	Anap
	D-α-methyllysine	Dmlys	N-benzylglycine	Nphe
	D-α-methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
15	D-α-methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
	D-α-methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
	D-α-methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
	D-α-methylserine	Dmser	N-cyclobutylglycine	Ncbut
	D-α-methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
20	D-α-methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
	D-α-methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
	D-α-methylvaline	Dmval	N-cylcododecylglycine	Ncdod
	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
25	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
	D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
	D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
	D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
	D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
30	D-N-methylhistidine	Dnmhis	N-(hydroxyethyl))glycine	Nser

	D-N-methylisoleucine	Dnmile	N-(imidazolylethyl))glycine	Nhis
	D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp
	D-N-methyllysine	Dnmlys	N-methyl-γ-aminobutyrate	Nmgabu
	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
5	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen
	N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
	N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
10	D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
	D-N-methyltyrosine	Dnmtyr	N-methyla-napthylalanine	Nmanap
	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	γ-aminobutyric acid	Gabu	N-(*p*-hydroxyphenyl)glycine	Nhtyr
	L-*t*-butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
15	L-ethylglycine	Etg	penicillamine	Pen
	L-homophenylalanine	Hphe	L-α-methylalanine	Mala
	L-α-methylarginine	Marg	L-α-methylasparagine	Masn
	L-α-methylaspartate	Masp	L-α-methyl-*t*-butylglycine	Mtbug
	L-α-methylcysteine	Mcys	L-methylethylglycine	Metg
20	L-α-methylglutamine	Mgln	L-α-methylglutamate	Mglu
	L-α-methylhistidine	Mhis	L-α-methylhomophenylalanine	Mhphe
	L-α-methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
	L-α-methylleucine	Mleu	L-α-methyllysine	Mlys
	L-α-methylmethionine	Mmet	L-α-methylnorleucine	Mnle
25	L-α-methylnorvaline	Mnva	L-α-methylornithine	Morn
	L-α-methylphenylalanine	Mphe	L-α-methylproline	Mpro
	L-α-methylserine	Mser	L-α-methylthreonine	Mthr
	L-α-methyltryptophan	Mtrp	L-α-methyltyrosine	Mtyr
	L-α-methylvaline	Mval	L-N-methylhomophenylalanine	Nmhphe
30	N-(N-(2,2-diphenylethyl)	Nnbhm	N-(N-(3,3-diphenylpropyl)	Nnbhe

carbamylmethyl)glycine		carbamylmethyl)glycine
1-carboxy-1-(2,2-diphenyl-ethylamino)cyclopropane	Nmbc	

Crosslinkers can be used, for example, to stabilize 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In addition, peptides can be conformationally constrained by, for example, incorporation of C_α and N $_\alpha$-methylamino acids, introduction of double bonds between C_α and C_β atoms of amino acids and the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two side chains or between a side chain and the N or C terminus.

The present invention further contemplates chemical analogs of the subject polypeptide capable of acting as antagonists or agonists of M-GRH or which can act as functional analogs of M-GRH. Chemical analogs may not necessarily be derived from the instant M-GRH molecules but may share certain conformational similarities. Alternatively, chemical analogs may be specifically designed to mimic certain physiochemical properties of the subject M-GRH molecules. Chemical analogs may be chemically synthesized or may be detected following, for example, natural product screening. The latter refers to molecules identified from various environmental sources such a river beds, coral, plants, microorganisms and insects.

These types of modifications may be important to stabilize the subject M-GRH molecules if administered to an individual or for use as a diagnostic reagent.

Other derivatives contemplated by the present invention include a range of glycosylation variants from a completely unglycosylated molecule to a modified glycosylated molecule.

Altered glycosylation patterns may result from expression of recombinant molecules in different host cells.

The present invention also provides a method for identifying a M-GRH, said method comprising screening a nucleotide database and identifying a nucleotide sequence having at least 60% similarity to SEQ ID NO:17 or SEQ ID NO:34 or SEQ ID NO:36 or SEQ ID NO:38 after optimal alignment.

Reference to a "nucleotide database" includes screening an existing genomic or cDNA or mRNA database or screening for a target nucleic acid molecule in a mammalian cell such as using oligonucleotide probes or primers, sequencing the target molecule and comparing the sequence to SEQ ID NO:17 or SEQ ID NO:34 or SEQ ID NO:36 or SEQ ID NO:38.

In an alternative method, a database of mammalian protein sequences is screened for an amino acid sequence having at least 60% similarity to the amino acid sequence encoded by SEQ ID NO:17 or SEQ ID NO:34 or SEQ ID NO:36 or SEQ ID NO:38. Again, a "database" includes a *de novo* protein sequence isolated and identified on a transcription factor isolated form a mammalian cell.

In yet another alternative, a M-*grh* or its protein product is deemed one which has at least about 60% similarity at the nucleotide level to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or at the amino acid level to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 or SEQ ID NO:15.

Still yet another aspect of the present invention provides a means of identifying a nucleotide sequence likely to encode an M-GRH transcription factor, said method comprising interrogating a mammalian genome database conceptually translated into different reading frames with an amino acid sequence defining *Drosophila GRH* or any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 and SEQ ID NO:16 and identifying a nucleotide sequence

corresponding to an amino acid sequence having at least about 60% similarity to *Drosophila GRH* or to any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 and SEQ ID NO:16.

Preferably, the genome is conceptually translated into from about 3 to about 6 reading frames and more preferably six reading frames.

It is proposed in accordance with the present invention that the M-GRH transcription factors are involved in the modulation of expression of a number of genes including developmentally regulated genes. Accordingly, aberrations in the M-GRH or M-*grh* molecules are proposed to cause over or under expression of particular genes leading to a potentially unwanted phenotype. The phenotype may manifest itself pre- or post-natally. A pre-natal manifestation includes at the embryo or fetus stage. Conditions contemplated include developmentally-determined disease conditions such as poor brain development, poor muscle or bone development, aberrations in facial or cranial structures, malformed spinal structures, predispositions to a range of cancers including melanomas and immunological disorders.

Accordingly, another aspect of the present invention contemplates a method for detecting an aberrant phenotype or a propensity for an aberrant phenotype to develop, said method comprising screening for a variation in a nucleotide sequence encoding a mammalian MGR, BOM and/or SOM or their homologs.

Reference herein to "MGR", "BOM" and "SOM" includes murine and human forms of these molecules such as human MGR p49 (SEQ ID NO:2), human MGR p70 (SEQ ID NO:4), human BOM (SEQ ID NO:6), human SOM (SEQ ID NO:8), murine MGR p61 (SEQ ID NO:10), murine MGR p70 (SEQ ID NO:12), murine BOM (SEQ ID NO:14) and murine SOM (SEQ ID NO:16).

A homolog of MGR, BOM and SOM is as herein defined including a molecule having at least about 60% amino acid sequence similarity to MGR, BOM or SOM or at least about

60% nucleic acid similarity to *mgr*, *bom* or *som* or a nucleic acid molecule capable of hybridizing to the coding strands of *mgr*, *bom* or *som* or complementary forms thereof under low stringency conditions.

Aberrations may also be detectable at the amino acid level when the mammalian homologs of *Drosophila grh* encode protein transcription factors.

Accordingly, another aspect of the present invention contemplates a method for detecting an aberrant phenotype or a propensity for an aberrant phenotype to develop, said method comprising screening for a variation in an amino acid sequence encoding MGR, BOM and/or SOM or their homologs.

As above, reference to MGR, BOM and SOM include amino acid sequences defining human MGR p49 (SEQ ID NO:2), human MGR p70 (SEQ ID NO:4), human BOM SEQ ID NO:6), human SOM (SEQ ID NO:8), murine MGR p61 (SEQ ID NO:10), murine MGR p70 (SEQ ID NO:12), murine BOM (SEQ ID NO:14) and murine SOM (SEQ ID NO:16).

As stated above, the mammalian transcription factors and their genetic sequences have a range of diagnostic and therapeutic utilities. The detection of an aberrant transcription factor or a nucleotide sequence encoding an aberrant transcription factor is indicative of a disease condition including a degenerative or developmental disease condition.

Any number of methods may be employed to detect aberrant transcription factors or their genetic sequences. Immunological testing is one particular method. Accordingly, the present invention extends to antibodies and other immunological agents directed to or preferably specific for the mammalian transcription factors or a fragment thereof. The antibodies may be monoclonal or polyclonal or may comprise Fab fragments or synthetic forms.

Specific antibodies can be used to screen for the subject mammalian transcription factors and/or their fragments. Techniques for the assays contemplated herein are known in the art and include, for example, sandwich assays and ELISA.

It is within the scope of this invention to include any second antibodies (monoclonal, polyclonal or fragments of antibodies or synthetic antibodies) directed to the first mentioned antibodies referred to above. Both the first and second antibodies may be used in detection assays or a first antibody may be used with a commercially available anti-immunoglobulin antibody. An antibody as contemplated herein includes any antibody specific to any region of the mammalian transcription factors.

Both polyclonal and monoclonal antibodies are obtainable by immunization with mammalian transcription factors or antigenic fragments thereof and either type is utilizable for immunoassays. The methods of obtaining both types of sera are well known in the art. Polyclonal sera are less preferred but are relatively easily prepared by injection of a suitable laboratory animal with an effective amount of subject polypeptide, or antigenic parts thereof, collecting serum from the animal and isolating specific sera by any of the known immunoadsorbent techniques. Although antibodies produced by this method are utilizable in virtually any type of immunoassay, they are generally less favoured because of the potential heterogeneity of the product.

The use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for monoclonal antibody production derived by fusing an immortal cell line and lymphocytes sensitized against the immunogenic preparation can be done by techniques which are well known to those who are skilled in the art.

Another aspect of the present invention contemplates, therefore, a method for detecting a mammalian transcription factor or fragment thereof in a biological sample from a subject, said method comprising contacting said biological sample with an antibody specific for said mammalian transcription factor or fragment thereof or its derivatives or homologs for

a time and under conditions sufficient for an antibody-polypeptide complex to form, and then detecting said complex.

A biological sample includes a cell extract.

Reference to a "mammalian transcription factor" is considered to be a reference to a homolog of *Drosophia grh*, i.e. M-GRH.

The presence of the instant mammalian transcription factors or their fragments may be detected in a number of ways such as by Western blotting and ELISA procedures. A wide range of immunoassay techniques are available as can be seen by reference to U.S. Patent Nos. 4,016,043, 4,424,279 and 4,018,653.

Sandwich assays are among the most useful and commonly used assays and are favoured for use in the present invention. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabeled antibody is immobilized on a solid substrate and the sample to be tested brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labeled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labeled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of hapten. Variations on the forward assay include a simultaneous assay, in which both sample and labeled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including any minor variations as will be readily apparent. In accordance with the present invention the sample is one which might contain a subject transcription factor including by tissue biopsy, blood, synovial fluid and/or lymph. The sample is,

therefore, generally a biological sample comprising biological fluid. The transcription factor is likely to be in blood or other fluid in the case where cell apoptosis is occurring.

In the typical forward sandwich assay, a first antibody having specificity for the instant polypeptide or antigenic parts thereof, is either covalently or passively bound to a solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (e.g. 2-40 minutes or where more convenient, overnight) and under suitable conditions (e.g. for about 20°C to about 40°C) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the hapten. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the hapten.

An alternative method involves immobilizing the target molecules in the biological sample and then exposing the immobilized target to specific antibody which may or may not be labeled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labelling with the antibody. Alternatively, a second labeled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

By "reporter molecule" as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-bound antibody. Detection may be either qualitative or quantitative. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores

or radionuclide containing molecules (i.e. radioisotopes) and chemiluminescent molecules. In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable colour change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labeled antibody is added to the first antibody hapten complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of hapten which was present in the sample. "Reporter molecule" also extends to use of cell agglutination or inhibition of agglutination such as red blood cells on latex beads, and the like.

Alternately, fluorescent compounds, such as fluorescein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labeled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. The fluorescent labeled antibody is allowed to bind to the first antibody-hapten complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength the fluorescence observed indicates the presence of the hapten of interest. Immunofluorescene and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

The present invention also contemplates genetic assays such as involving PCR analysis to detect RNA expression products of a genetic sequence encoding a mammalian transcription factor. The genetic assays may also be able to detect nucleotide polymorphisms or other substitutions, additions and/or deletions in the nucleotide sequence of a mammalian transcription factor. Changes in levels of mammalian transcription factor expression such as following mutations in the promoter or regulatory regions or loss of mammalian transcription factor activity following mutations in mammalian transcription factor nucleotides is proposed to be indicative of a disease condition or a propensity for a disease condition to develop. For example, a cell biopsy could be obtained and DNA or RNA extracted. Alternative methods which may be used alone or in conjunction with other methods include direct nucleotide sequencing or mutation scanning such as single stranded conformation polymorphoms analysis (SSCP) as well as specific oligonucleotide hybridization, denaturing high performance liquid chromatography, first nucleotide change (FNC) amongst others.

The present invention extends to polymorphisms which in the M-*grh* genes leads to healthy or abnormal phenotypes.

The present invention further contemplates kits to facilitate the rapid detection of mammalian transcription factors or their fragments in a subject's biological fluid.

Again, a biological fluid includes a cell extract such as a DNA/RNA extract.

Still yet another aspect of the present invention contemplates genomic sequences including gene sequences encoding a mammalian transcription factor as well as regulatory regions such as promoters, terminators and transcription/translation enhancer regions associated with the gene encoding a mammalian transcription factor.

The term "gene" is used in its broadest sense and includes cDNA corresponding to the exons of a gene. Accordingly, reference herein to a "gene" is to be taken to include:-

(i) a classical genomic gene consisting of transcriptional and/or translational regulatory sequences and/or a coding region and/or non-translated sequences (i.e. introns, 5'- and 3'- untranslated sequences); or

(ii) mRNA or cDNA corresponding to the coding regions (i.e. exons) and 5'- and 3'- untranslated sequences of the gene.

The term "gene" is also used to describe synthetic or fusion molecules encoding all or part of an expression product. In particular embodiments, the term "nucleic acid molecule" and "gene" may be used interchangeably.

In a particularly useful embodiment, the present invention provides a promoter for the mammalian transcription factor gene. The identification of the promoter permits developmentally-regulated expression of particular genetic sequences. The latter would include a range of therapeutic molecules such as cytokines, growth factors, antibiotics or other molecules to assist in the treatment of particular disease conditions.

Accordingly, another aspect of the present invention provides a M-*grh*-specific promoter or functional derivative or homolog thereof, said promoter *in situ* operably linked to a nucleotide sequence comprising any one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or their complementary forms or a nucleotide sequence having at least about 60% similarity to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or their complementary forms or a nucleotide sequence capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or their complementary forms under low stringency conditions.

The promoter is conveniently resident in a vector which comprises unique restriction sites to facilitate the introduction of genetic sequences operably linked to the promoter.

All such constructs are useful in order to produce recombinant M-GRH molecules and/or in gene therapy protocols.

The present invention further contemplates a genetically modified animal.

More particularly, the present invention provides an animal model useful for screening for agents capable of ameliorating the effects of an aberrant M-GRH or M-*grh* gene. In one embodiment, the animal model produces low amounts of M-*grh*. Such an animal would have a predisposition for a range of diseases including developmentally regulated diseases. The animal model is useful for screening for agents which ameliorate such conditions.

Accordingly, another aspect of the present invention provides a genetically modified animal wherein said animal produces low amounts of M-*grh* relative to a non-genetically modified animal of the same species. Reference to "low amounts" includes zero amounts or up to about 10% lower than normalized amounts.

Preferably, the genetically modified animal is a mouse, rat, guinea pig, rabbit, pig, sheep or goat. More preferably, the genetically modified animal is a mouse or rat. Most preferably, the genetically modified animal is a mouse.

Accordingly, a preferred aspect of the present invention provides a genetically modified mouse wherein said mouse produces low amounts of M-*grh* relative to a non-genetically modified mouse of the same strain.

The animal model contemplated by the present invention comprises, therefore, an animal which is substantially incapable of producing a M-*grh*. Generally, but not exclusively, such an animal is referred to as a homozygous or heterozygous M-*grh*-knockout animal.

The animal models of the present invention may be in the form of the animals or may be, for example, in the form of embryos for transplantation. The embryos are preferably maintained in a frozen state and may optionally be sold with instructions for use.

The genetically modified animals may also produce larger amounts of M-GRH For example, over expression of normal M-*grh* or mutant M-*grh* may produce dominant negative effects and may become useful disease models.

Accordingly, another aspect of the present invention is directed to a genetically modified animal over-expressing genetic sequences encoding M-*grh*.

A genetically modified animal includes a transgenic animal, or a "knock-out" or "knock-in" animal.

Yet another aspect of the present invention provides a targeting vector useful for inactivating a gene encoding M-GRH, said targeting vector comprising two segments of genetic material encoding said M-GRH flanking a positive selectable marker wherein when said targeting vector is transfected into embryonic stem (ES) cells and the marker selected, an ES cell is generated in which the gene encoding said M-GDH is inactivated by homologous recombination.

Preferably, the ES cells are from mice, rats, guinea pigs, pigs, sheep or goats. Most preferably, the ES cells are from mice.

Still yet another aspect of the present invention is directed to the use of a targeting vector as defined above in the manufacture of a genetically modified animal substantially incapable of producing M-GRH.

Even still another aspect of the present invention is directed to the use of a targeting vector as defined above in the manufacture of a genetically modified mouse substantially incapable of producing M-GRH.

Preferably, the vector is DNA. A selectable marker in the targeting vector allows for selection of targeted cells that have stably incorporated the targeting DNA. This is especially useful when employing relatively low efficiency transformation techniques such as electroporation, calcium phosphate precipitation and liposome fusion where typically fewer than 1 in 1000 cells will have stably incorporated the exogenous DNA. Using high efficiency methods, such as microinjection into nuclei, typically from 5-25% of the cells will have incorporated the targeting DNA; and it is, therefore, feasible to screen the targeted cells directly without the necessity of first selecting for stable integration of a selectable marker. Either isogenic or non-isogenic DNA may be employed.

Examples of selectable markers include genes conferring resistance to compounds such as antibiotics, genes conferring the ability to grow on selected substrates, genes encoding proteins that produce detectable signals such as luminescence. A wide variety of such markers are known and available, including, for example, antibiotic resistance genes such as the neomycin resistance gene (*neo*) and the hygromycin resistance gene (*hyg*). Selectable markers also include genes conferring the ability to grow on certain media substrates such as the *tk* gene (thymidine kinase) or the *hprt* gene (hypoxanthine phosphoribosyltransferase) which confer the ability to grow on HAT medium (hypoxanthine, aminopterin and thymidine); and the bacterial *gpt* gene (guanine/xanthine phosphoribosyltransferase) which allows growth on MAX medium (mycophenolic acid, adenine and xanthine). Other selectable markers for use in mammalian cells and plasmids carrying a variety of selectable markers are described in Sambrook *et al.*, *Molecular Cloning - A Laboratory Manual*, Cold Spring Harbour, New York, USA, 1990.

The preferred location of the marker gene in the targeting construct will depend on the aim of the gene targeting. For example, if the aim is to disrupt target gene expression, then the selectable marker can be cloned into targeting DNA corresponding to coding sequence in the target DNA. Alternatively, if the aim is to express an altered product from the target gene, such as a protein with an amino acid substitution, then the coding sequence can be

modified to code for the substitution, and the selectable marker can be placed outside of the coding region, for example, in a nearby intron.

The selectable marker may depend on its own promoter for expression and the marker gene may be derived from a very different organism than the organism being targeted (e.g. prokaryotic marker genes used in targeting mammalian cells). However, it is preferable to replace the original promoter with transcriptional machinery known to function in the recipient cells. A large number of transcriptional initiation regions are available for such purposes including, for example, metallothionein promoters, thymidine kinase promoters, β-actin promoters, immunoglobulin promoters, SV40 promoters and human cytomegalovirus promoters. A widely used example is the pSV2-*neo* plasmid which has the bacterial neomycin phosphotransferase gene under control of the SV40 early promoter and confers in mammalian cells resistance to G418 (an antibiotic related to neomycin). A number of other variations may be employed to enhance expression of the selectable markers in animal cells, such as the addition of a poly(A) sequence and the addition of synthetic translation initiation sequences. Both constitutive and inducible promoters may be used.

The DNA is preferably modified by homologous recombination. The target DNA can be in any organelle of the animal cell including the nucleus and mitochondria and can be an intact gene, an exon or intron, a regulatory sequence or any region between genes.

Homologous DNA is a DNA sequence that is at least 70% identical with a reference DNA sequence. An indication that two sequences are homologous is that they will hybridize with each other under stringent conditions (Sambrook *et al.*, 1990, *supra*).

The present invention further contemplates co-suppression (i.e. sense suppression) and antisense suppression to down-regulate expression of M-*grh* This would generally occur in a target test animal such as to generate a disease model.

In addition to providing a diagnostic capability as described above, the isolated nucleic

acid molecules of the present invention may also provide a therapeutic capability by being used to correct or complement an abnormality detected in a subject. To deliver the appropriate sequence to a recipient cell or tissue of a subject, an isolated nucleic acid molecule of the present invention may be cloned into a suitable genetic construct such as a suitable vector.

Accordingly, a further aspect of the present invention contemplates a genetic construct comprising a nucleotide sequence encoding an M-*grh* selected from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or a variant thereof or a nucleotide sequence having at least 60% similarity to one or more of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 or a variant thereof or a nucleotide sequence capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 or SEQ ID NO:15 under low stringency conditions or a variant thereof or a complementary form thereof.

A "vector" is a polynucleotide molecule, preferably a DNA molecule derived, for example, from a plasmid, bacteriophage, or plant virus, into which a polynucleotide can be inserted or cloned. A vector preferably contains one or more unique restriction sites and can be capable of autonomous replication in a defined host cell including a target cell or tissue or a progenitor cell or tissue thereof, or be integrable with the genome of the defined host such that the cloned sequence is reproducible. Accordingly, the vector may be an autonomously replicating vector, i.e. a vector that exists as an extra-chromosomal entity, the replication of which is independent of chromosomal replication. Examples include a linear or closed circular plasmid, an extra-chromosomal element, a mini-chromosome, or an artificial chromosome. The vector may also contain a means for assuring self-replication. Alternatively, the vector may be one which, when introduced into the host cell, is integrated into the genome and replicated together with the chromosome(s) into which it has been integrated. A vector system may comprise a single vector or plasmid, two or more vectors or plasmids, which together contain the total DNA to be introduced into the genome of the host cell, or a transposon.

Vectors suitable for gene therapy applications are well known in the art. The choice of the vector will typically depend on the compatibility of the vector with the host cell into which it is to be introduced. The vector may also include an additional genetic construct comprising a selection marker such as an antibiotic resistance gene that can be used for selection of suitable transformants. Examples of such resistance genes are known to those skilled in the art and include the *nptII* gene that confers resistance to the antibiotics kanamycin, and G418 (Geneticin®) and the *hph* gene which confer resistance to the antibiotic hygromycin B.

Accordingly, in a related embodiment, the present invention provides a genetic construct comprising a promoter or functional equivalent thereof operably linked to a nucleotide sequence of the invention.

Reference herein to a "promoter" is to be taken in its broadest context and includes the transcriptional regulatory sequences of a classical genomic gene, which is required for accurate transcription initiation, with or without a CCAAT box sequence and additional regulatory elements (i.e. upstream activating sequences, enhancers and silencers), which alter gene expression in response to developmental and/or external stimuli, or in a tissue-specific manner. A promoter is usually, but not necessarily, positioned upstream (5') of a gene region, the expression of which it regulates. Furthermore, the regulatory elements comprising a promoter are usually positioned within 2 kb of the start site of transcription of the gene. As is known in the art, some variation in this distance can be accommodated without loss of promoter function.

The selection of an appropriate promoter sequence to regulate expression of a transcription factor encoded by an isolated nucleic acid molecule of the present invention is an important consideration. Examples of suitable promoters include viral, fungal, bacterial, animal and plant derived promoters capable of functioning in eukaryotic animal cells and, especially, human cells. The promoter may regulate the expression of the nucleic acid molecule differentially with respect to the cell, tissue or organ in which expression occurs,

or with respect to the developmental stage at which expression occurs.

Preferably, the promoter is capable of regulating expression of a nucleic acid molecule in a eukaryotic cell, tissue or organ, at least during the period of time over which the regulated gene is expressed therein, and more preferably also immediately preceding the commencement of detectable expression of the regulated gene in said cell, tissue or organ.

Particularly preferred promoters for use with the nucleic acid molecules of the present invention include the bacteriophage T7 promoter, bacteriophage T3 promoter, SP6 promoter, *lac* operator-promoter, *tac* promoter, SV40 late promoter, SV40 early promoter, RSV-LTR promoter, CMV IE promoter, CaMV 35S promoter, SCSV promoter, SCBV promoter and the like. Those skilled in the art will readily be aware of additional promoter sequences other than those specifically described.

In the present context, the terms "in operable connection with" or "operably linked" or similar shall be taken to indicate that expression of the nucleic acid molecule is under the control of the promoter sequence, with which it is spatially connected, in a cell, tissue, organ or whole organism.

The genetic construct of the present invention may also comprise a 3' non-translated sequence. A 3' non-translated sequence refers to that portion of a gene comprising a DNA segment that contains a polyadenylation signal and any other regulatory signals capable of effecting mRNA processing or gene expression. The polyadenylation signal is characterized by effecting the addition of polyadenylic acid tracts to the 3' end of the mRNA precursor. Polyadenylation signals are commonly recognized by the presence of homology to the canonical form 5' AATAAA-3' although variations are not uncommon.

Accordingly, a genetic construct comprising a nucleic acid molecule of the present invention, operably linked to a promoter, may be cloned into a suitable vector for delivery to a cell or tissue in which regulation is faulty, malfunctioning or non-existent, in order to rectify and/or provide the appropriate regulation. Vectors comprising appropriate genetic

constructs may be delivered into target eukaryotic cells by a number of different means well known to those skilled in the art of molecular biology.

The present invention further contemplates the use of an M-GRH or M-*grh* in the manufacture of a medicament for the treatment of a disease condition in a mammal such as a human.

The present invention is further directed to promoters and 3'- and 5'-regulatory regions associated with genomic forms of M-*grh* genes. These regions can be readily identified by, for example, chromosome walking using M-*grh* nucleic acid molecules or probes or primers therefrom.

The present invention is further described by the following non-limiting Examples.

EXAMPLE 1

Polymerase chain reaction

For RT-PCR , first strand cDNA was prepared from 2 μg of mRNA from primary tissues using random hexamers. Each cDNA sample was appropriately diluted to give similar amplification of S14 RNA under the same PCR conditions. The primer sequences are detailed below. The PCR conditions were 94°C for 2 min followed by 35 cycles of 94°C for 30 sec, 60°C for 30 sec and 72°C for 45 sec with a final extension at 72°C for 5 min. All PCR products were electrophoresed on 1.5% w/v agarose gels, transferred to nitrocellulose and analyzed by Southern blot using ^{32}P-radiolabeled internal oligonucleotides as probes. Membranes were then autoradiographed for 2 hr at -70°C.

The following primers were used to amplify probes for cDNA library screening and for RT-PCR:-

human p49 mgr

5'-GAAGTCTTTGATGCCCTGATG-3' [SEQ ID NO:19]

5'-AACCCATTCCCTCGACATAGA-3' [SEQ ID NO:20]

human p70 mgr

5-AGCGCGATGACACAGGAGTA-3' [SEQ ID NO:21]

5'-CGTTGCTATGGAGACAGTGA-3' [SEQ ID NO:22]

human bom

5'-CCGTTTAACAAGGACACTGC-3' [SEQ ID NO:23]

5'-CTGGAAGCCACCAAATCTCT-3' [SEQ ID NO:24]

murine p70 mgr

5'-AGCGCGATGACACAGGAGTA-3' [SEQ ID NO:25]

5'-AGTGCCAGAGCTGAACTGAT-3' [SEQ ID NO:26]

murine p61 mgr

5'-TCCATGGGTTCCTTGAGTTC-3' [SEQ ID NO:27]

5'-AGTGCCAGAGCTGAACTGAT'-3' [SEQ ID NO:28]

murine bom

5'-AAAGGGGAGCGAGTTCATTG-3' [SEQ ID NO:29]

5'-AGAGCTCTCGGTGATGGATA-3' [SEQ ID NO:30]

EXAMPLE 2

Cloning of human and murine mgr and bom

Human p49 *mgr* was cloned from a fetal brain cDNA phage library in the λZAP II vector (Stratagene). The cDNA encoding the longer human MGR isoform was amplified by RT-PCR from human kidney mRNA. The cDNA encoding the smaller murine isoform of MGR was cloned from a 17.5-day embryo phage library in the Lambda TripelEx vector (Clontech). The murine p70 cDNA was amplified from murine kidney mRNA by RT-PCR. The human *bom* cDNA was isolated form a placental phage library in the Lambda ZAP II vector (Stratagene) and the murine cDNA from an embryonic carcinoma cell line (P19) phage library in the Uni-ZAP XR vector (Stratagene). The murine MGR genomic locus was obtained from a 129SVJ phage library in the Lambda FIX II vector (Stratagene).

From similarity searches of GenBank databases, using the GRH protein sequence as a query, two murine expressed sequence tag (EST) entries were found from adult brain and ovary and one human EST entry from fetal brain that were not identical to any previously reported genes, yet shared high degrees of homology with each other and *grh*. These sequences were used to design murine and human primers and amplified probes from murine adult brain and ovary and human adult brain cDNA. The murine probe from adult brain cDNA was used in a screen of a day 17.5 mouse embryo cDNA library to obtain a full length clone of a gene referred to as mammalian *grainyhead* (*mgr*) due to its sequence and functional homology and similar expression pattern to that of the fly gene. The human

probe derived from adult brain cDNA was used to obtain a full length cDNA clone from a human fetal brain library. Amino acid sequence comparison reveals this to be the human homolog of MGR with 94% identity at the amino acid level.

The murine probe derived from ovary cDNA was used in a screen of a murine teratocarcinoma cell line (P19) cDNA library to obtain a full length clone of a novel gene distinct from but highly related to *mgr* named *brother-of-mgr* (*bom*). The homology between *mgr* and *bom* suggests that *mgr* and *bom* arose through gene duplication.

The human homolog of *bom* was obtained using primers derived from a high throughput genome sequencing (HTGS) database entry with homology to murine *bom*. These were used to amplify a probe from a human placental cDNA library that was then screened to yield a full length human cDNA clone. Amino acid sequence comparison between murine and human BOM revealed 94% identity.

The sequence alignments between *grh, mgr, bom, CP2* and *LBP-1a* revealed that *mgr* and *bom* are more closely related to *grh* than the previously identified homologs CP2 and LBP-1a (Table 4). This homology is particularly evident in the DNA binding and dimerization domains emphasizing the importance of protein/protein and protein/DNA interactions for the function of these factors.

TABLE 4 Amino acid sequence comparison of GRH-like genes and *Drosophila grh*

Amino acid identity/ similarity to Grainyhead (%)	Overall	DNA-binding domain	Dimerization domain
MGR	37/52	48/64	39/61
BOM	35/52	46/63	37/61
SOM	33/48	42/60	38/57
CP2	26/42	32/52	29/47
LBP-1a	23/39	31/51	28/43

EXAMPLE 3

Identification of a second isoform of MGR

A striking feature of the alignment between MGR and BOM was the absence of an MGR domain corresponding to the first 93 amino acids of BOM. In view of the absence of tissue-specific isoforms of GRH, the EST database was searched for similar sequences using the 5' end of *bom* as a query. A highly similar but non-identical sequence in an EST from murine kidney was located. The most 3' 30 nucleotides of this EST was identical to 30 nucleotides close to the 5' end of the *mgr*. Based on this, primers were designed from the kidney EST and *mgr* cDNA sequences and amplified a product of the predicted size from murine kidney cDNA. A similar product was also amplified from human kidney cDNA. Amino acid sequence analysis of the murine product revealed that it was highly homologous to the 5' end of the BOM protein and contiguous with the *mgr* open reading frame. However, it lacked the first 11 amino acids of a previously isolated *mgr* clone suggesting the presence of alternate splicing. To examine this, the murine *mgr* genomic locus was isolated and mapped. As shown in Figure 1B, the first three coding exons in the locus are exclusive to the p70 isoform of *mgr*. In contrast, the shorter isoform of *mgr*'s (p61) first coding exon is absent in the p70 isoform. Significantly, the 5' end of this exon lacks a splice acceptor site explaining its absence from the longer isoform. Instead, promoter sequences with a clear TATA box and CAP site are evident in close proximity to the translation initiation site (Figure 1C). Subsequent mapping of the human genomic locus revealed that murine exon four was conserved in the human p70 protein but was absent in

the 49 kDa isoform of MGR.

EXAMPLE 4

The first three exons of the mgr genomic locus encode transcriptional activation domain

Although significant sequence homology exists between *grh* and the shorter *mgr* isoforms and p70 *mgr*, the isoleucine rich transcriptional activation domain identified in the fly protein is not conserved. Examination of the MGR-coding sequences failed to reveal a region homologous to other known transactivation domains. In view of the high degree of conservation of the first three coding exons of p70 *mgr* and *bom*, it was postulated that this could be the functional domain responsible for activation. To address this, the cDNA fragment encoding the first 93 amino acids of human p70 MGR (encoded by the first three exons) was subcloned in frame with the GAL4 DNA binding domain in a mammalian expression vector. The comparable region of BOM and the full length p49 MGR cDNA in frame into this vector was also cloned. These plasmids were co-transfected into the human 293T cell line with a reporter plasmid containing five concatamerized GAL4 DNA binding sites upstream of the chloramphenicol acetyltransferase (CAT) gene. The vector containing only the GAL4 DNA-BD or containing the VP16 activation domain fused to the GAL DNA-BD served as the negative and positive controls, respectively. As shown in Figure 3, transcriptional activation of the CAT gene was observed with VP16, p70 MGR and the *bom* containing plasmids. No activation was observed with p49 *mgr* or the empty vector. These findings confirm the presence of a highly conserved activation domain in the p70 *mgr* and *bom* that is lacking in p49 *mgr*.

EXAMPLE 5

MGR binds to known GRH binding sites

To determine the extent of the functional homology between GRH and MGR, it was initially examined whether the mammalian protein could bind to the well-characterized binding sites for the *Drosophila* factor in the *Dopa decarboxylase* and *PCNA* gene

regulatory regions (Uv *et al., Mol. Cell. Biol. 17:* 6727-6735, 1997; Hayashi *et al., J. Biol. Chem. 274:* 35080-35088, 1999). Oligonucleotide probes encompassing these sites were incubated with nuclear extract from the human placental cell line JEG-3, which expresses both isoforms of MGR at RNA and protein level and analyzed in an electrophoretic mobility shift assay (EMSA).

EMSA were performed as previously described (Jane *et al., EMBO J. 14:* 97-105, 1995) with the following oligonucleotide probes (sense strand only given): *Drosophila dopa decarboxylase* promoter (Uv *et al.*, 1997, *supra*) - GGTGGTGCTCTAATAACCGGTTT-CCAAGATGCGC (SEQ ID NO:31]; *Drosophila PCNA* promoter (Hayashi *et al.*, 1999, *supra*) - GGGTAAAAAGTGTGAACAATCAAACCAGTTGGCA (SEQ ID NO:32]; human Engrailed-1 promoter (Logan *et al., Dev. Genet. 13:* 345-358, 1992) - GGACACACACCCAAACCCACACCCACCCACAAACACACAAACCGGCAGTGAC AACAACCACCCATCCTTCAATAACAGCAACCA [SEQ ID NO:33]. In some assays, anti-MGR polyclonal antiserum was included in the reaction mix. Two antisera were used for this purpose: antisera 611 - raised against peptides common to the p70 and p49 MGR proteins in the dimerization domain; and antisera 67 raised against unique peptides in the NH_2-terminal domain of p70 MGR. Nuclear extract for these assays was obtained from the human placental cell line, JEG-3.

As shown in Figure 2A, a specific protein/DNA complex was observed with the *PCNA* probe in the presence of pre-immune sera (lanes 1 and 3). This complex was supershifted with the addition of anti-p70 specific antisera raised against peptides in the amino terminal region of the protein (lane 4) and ablated with the addition of anti-MGR antisera raised against peptides common to p49 and p70 MGR in the dimerization domain of the protein (lane 2). Neither antisera cross-reacted with BOM. Similar results were obtained with the *Dopa decarboxylase* promoter probe (Figure 2B).

EXAMPLE 6

MGR binds to the human Engrailed-1 promoter

Many *Drosophila* genes regulated by GRH have known mammalian homologs. In terms of functional homology, Engrailed-1 (En-1) is one of the bests characterized. The En-1 promoter was, therefore, examined for the *grainyhead* consensus DNA binding sequence derived from a comparison of the *Drosophila Ultrabithorax, Dopa decarboxylase* and *fushi tarazu* promoters (Dynlacht *et al., Genes Dev. 3:* 1677-1688, 1989). As shown in Figure 3A, a highly conserved region was identified in the proximal En-1 promoter. Moreover, this sequence was also largely conserved in the DNAseI footprint attributed to *grh* in the *Drosophila engrailed* promoter (Soeller *et al., Genes Dev. 2:* 68-81, 1988). The ability of this region of the human En-1 promoter to compete off MGR binding to the *Ddc* probe (Figure 3B) in an EMSA with nuclear extract from JEG-3 cells was examined. As shown in Figure 3B, the specific MGR/DNA complex observed with the *Ddc* probe (lane 1) was supershifted with the addition of MGR antisera 67 (lane 2) and ablated with the addition of a 50-fold excess of unlabeled *Ddc* probe as competitor (lane 3). Addition of a 10- (lane 4) or 20-fold (lane 5) excess of unlabeled En-1 probe also markedly reduced the binding of MGR to the *Ddc* probe.

EXAMPLE 7

MGR activates transcription

To determine the functional significance of this binding, this region of the En-1 promoter was linked to a minimal globin gene promoter/luciferase reporter gene construct and transfected it into the MGR null cell line COS, in the presence of p70 MGR mammalian expression vector or the empty vector. Transfection of the minimal promoter/reporter or the TK promoter linked to a Renilla luciferase gene with either vector served as the controls. As shown in Figure 3C, expression of p70 MGR dramatically enhanced the transcriptional activity of the En-1 promoter (solid bars) but not the control minimal promoter (open bars) or the TK promoter (hatched bars).

EXAMPLE 8

Cloning of full-length human SOM

Human SOM was cloned using primers derived from a high through-put genomic sequence (HTGS) and a human expression sequence tag (EST) obtained from GenBank databases which, respectively, aligned with the dimerization domain and the activation domain of other MGR members. Using nested RT-PCR and human tonsil cDNA, another contig spanning 1300 nucleotides was obtained.

Utilizing 5' RACE, further oligoprimers and human testis cDNA, a 210 nucleotide sequence incorporating the initiating ATG was obtained. A contig of these overlapping sequences revealed the full length human SOM which upon alignment with other existing MGR family members showed >60% similarity at the protein level with conservation at the 5' activation, DNA-binding and dimerization domains.

EXAMPLE 9

Cloning of full-length murine SOM

A murine EST (GenBank) from optic cup tissue was identified, which when aligned with other murine homologs of the MGR family showed 70% similarity at the amino acid level, in the region of the DNA binding domain. Using semi-nested RT-PCR with murine testis cDNA, a 286 nucleotide sequence was amplified, cloned and sequenced for use as a probe.

Subsequently, a murine brain cDNA library (Stratagene) was screened. One clone was taken through to quaternary stage. This clone was excised from λZAP II vector into pBluescript and sequenced in both directions. A 1200 nucleotide length sequence was obtained, whichi lacked the 5' end. This was subsequently identified using 5' RACE from murine testis cDNA. A contig of these two sequences revealed the full length murine SOM.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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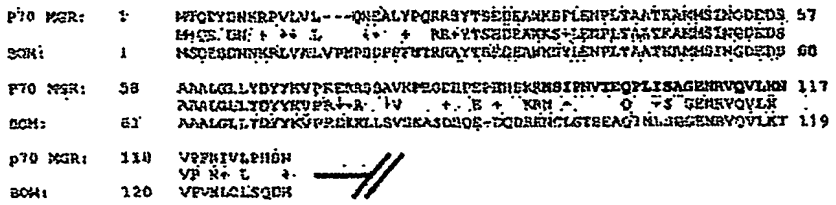

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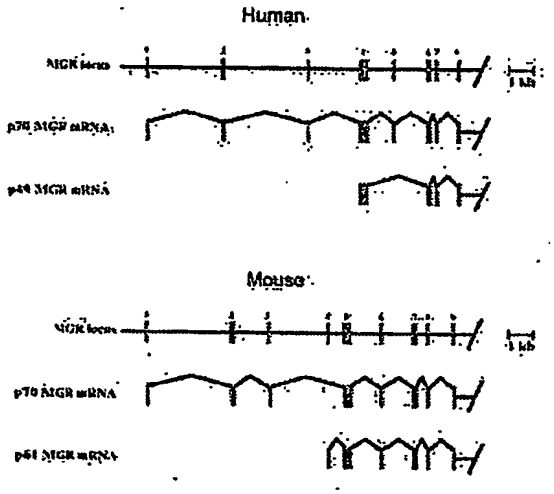

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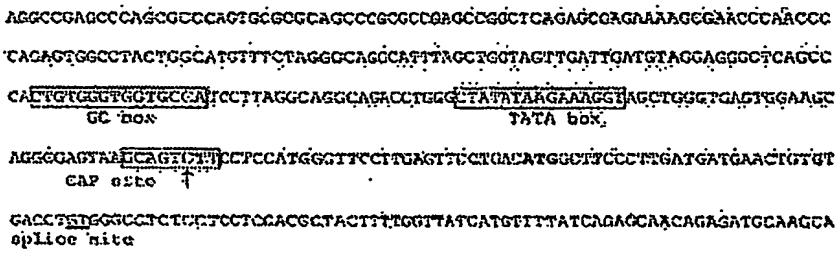

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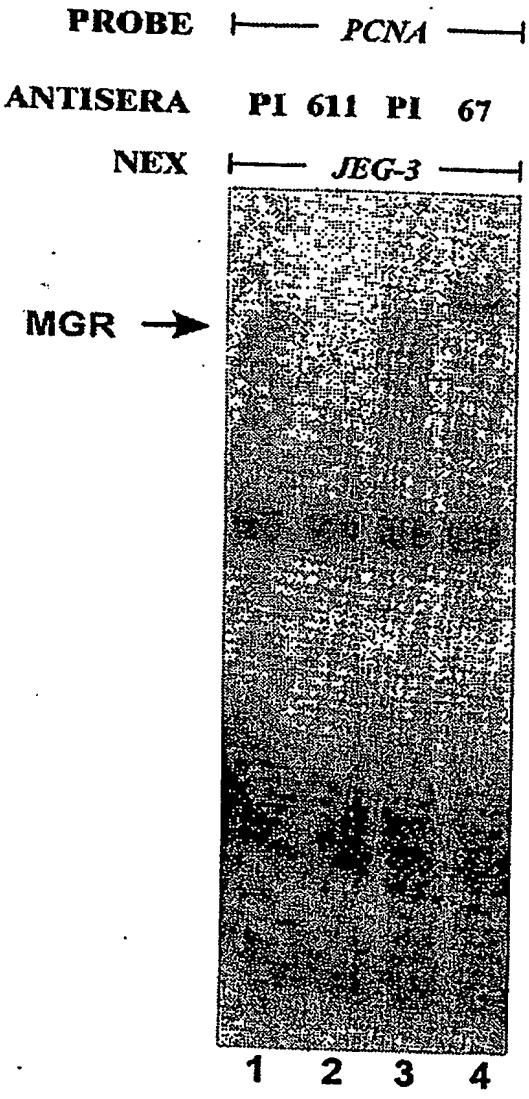

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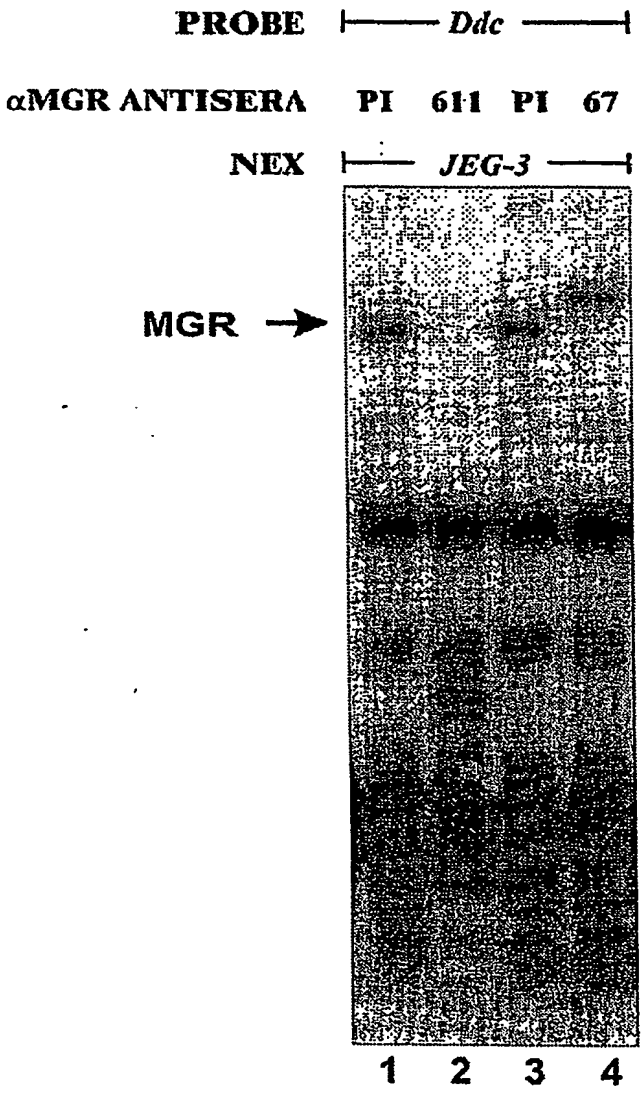

Figure 2B

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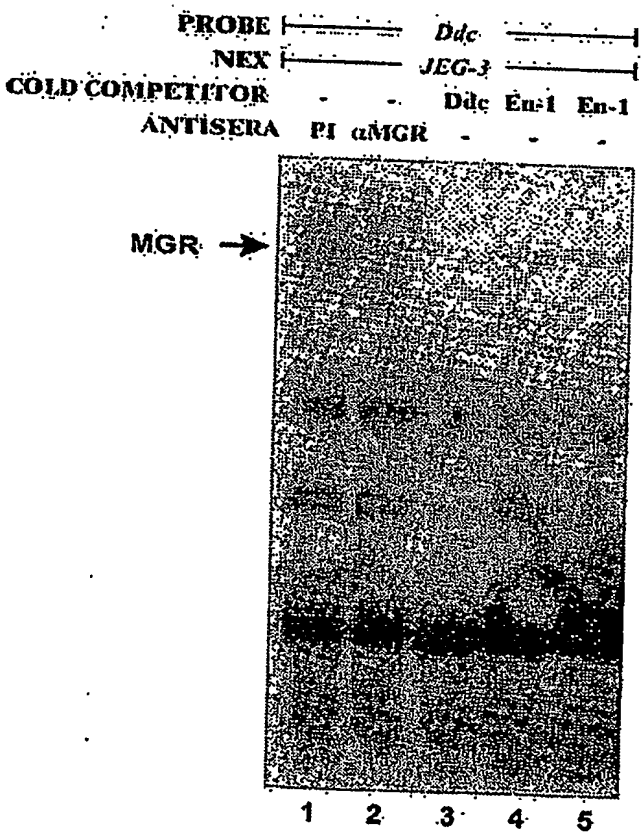
Figure 3A



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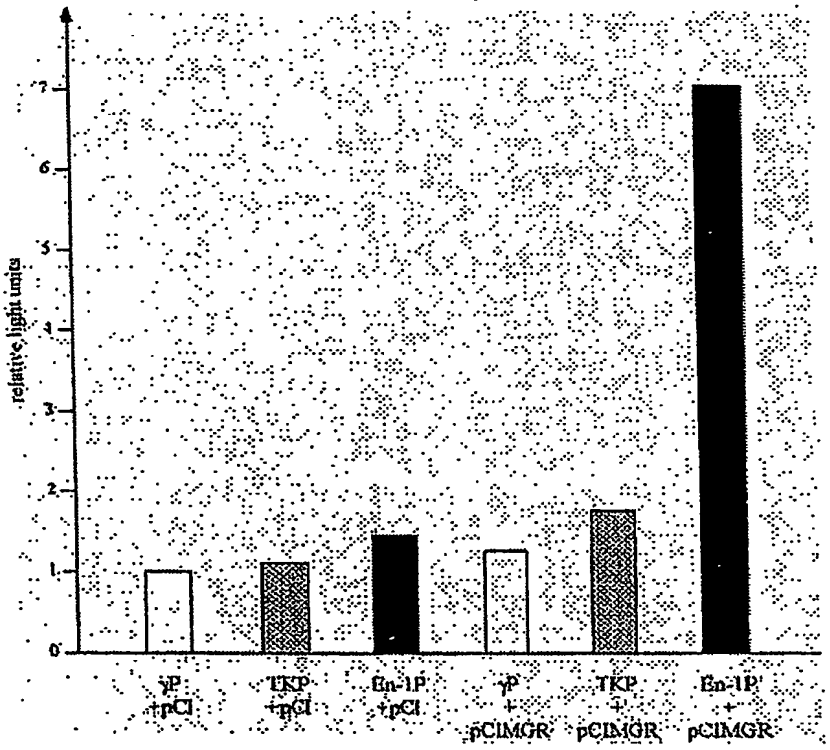
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Figure 3C

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gtg aag cat tac tcc aat gag gac acc ttc cag ctg cag att gaa gaa      1824
Val Lys His Tyr Ser Asn Glu Asp Thr Phe Gln Leu Gln Ile Glu Glu
                595                 600                 605

gcc ggg ggg tct tac aag ctc acc ctg acg gag atc taaaggcctg           1870
Ala Gly Gly Ser Tyr Lys Leu Thr Leu Thr Glu Ile
            610                 615

cgggccacag ctccccagga gttcagtgca ggtgtttcta gatcttacgg tttggcaact    1930

gcaggtaacc ccagtcagcc atgtcgccag cacaggtcta tgtcgaggga atgggttcct    1990

tgcaggttgg aggcggggct gcatctggct tggtggtagc atttaatcta ttgcattggt    2050

gtttttcaga tgaaagagaa atccatatac cattatgttt gaatttcctg atatatacag    2110

gatttaaagt gaaaacttta ttccaagagt taacagagtc tctgggaagc tttaggacat    2170

ctgctacgtt atttatcaaa atattgggat ctctgccttg tgcctacagt gtcgtgggcc    2230

tgctcgctag cagaagtcag aaaaggcgat aggcttggct ttaaggattt cgtgcccttg    2290

cctgaattca gtacaactcc actgcctcac gttagcggga gcgcacctga agagtacggg    2350

gggagccctc t                                                         2361

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<213>  human

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<221>  misc_feature
<222>  (342)..(342)
<223>  The 'Xaa' at location 342 stands for Lys, or Ile.

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Met Thr Gln Glu Tyr Asp Asn Lys Arg Pro Val Leu Val Leu Gln Asn
1               5                   10                  15

Glu Ala Leu Tyr Pro Gln Arg Arg Ser Tyr Thr Ser Glu Asp Glu Ala
            20                  25                  30

Trp Lys Ser Phe Leu Glu Asn Pro Leu Thr Ala Ala Thr Lys Ala Met
        35                  40                  45

Met Ser Ile Asn Gly Asp Glu Asp Ser Ala Ala Ala Leu Gly Leu Leu
    50                  55                  60

Tyr Asp Tyr Tyr Lys Val Pro Arg Glu Arg Arg Ser Ser Thr Ala Lys
65                  70                  75                  80
```

Pro Glu Val Glu His Pro Glu Pro Asp His Ser Lys Arg Asn Ser Ile
85 90 95

Pro Ile Val Thr Glu Gln Pro Leu Ile Ser Ala Gly Glu Asn Arg Val
100 105 110

Gln Val Leu Lys Asn Val Pro Phe Asn Ile Val Leu Pro His Gly Asn
115 120 125

Gln Leu Gly Ile Asp Lys Arg Gly His Leu Thr Ala Ser Asp Thr Thr
130 135 140

Val Thr Val Ser Ile Ala Thr Met Pro Thr His Ser Ile Lys Thr Glu
145 150 155 160

Thr Gln Pro His Gly Phe Ala Val Gly Ile Pro Pro Ala Val Tyr His
165 170 175

Pro Glu Pro Thr Glu Arg Val Val Val Phe Asp Arg Asn Leu Asn Thr
180 185 190

Asp Gln Phe Ser Ser Gly Ala Gln Ala Pro Asn Ala Gln Arg Arg Thr
195 200 205

Pro Asp Ser Thr Phe Ser Glu Thr Phe Lys Glu Gly Val Gln Glu Val
210 215 220

Phe Phe Pro Ser Asp Leu Ser Leu Arg Met Pro Gly Met Asn Ser Glu
225 230 235 240

Asp Tyr Val Phe Asp Ser Val Ser Gly Asn Asn Phe Glu Tyr Thr Leu
245 250 255

Glu Ala Ser Lys Ser Leu Arg Gln Lys Pro Gly Asp Ser Thr Met Thr
260 265 270

Tyr Leu Asn Lys Gly Gln Phe Tyr Pro Ile Thr Leu Lys Glu Val Ser
275 280 285

Ser Ser Glu Gly Ile His His Pro Ile Ser Lys Val Arg Ser Val Ile
290 295 300

Met Val Val Phe Ala Glu Asp Lys Ser Arg Glu Asp Gln Leu Arg His
305 310 315 320

Trp Lys Tyr Trp His Ser Arg Gln His Thr Ala Lys Gln Arg Cys Ile
325 330 335

Asp Ile Ala Asp Tyr Xaa Glu Ser Phe Asn Thr Ile Ser Asn Ile Glu
340 345 350

Glu Ile Ala Tyr Asn Ala Ile Ser Phe Thr Trp Asp Ile Asn Asp Glu
355 360 365

Ala Lys Val Phe Ile Ser Val Asn Cys Leu Ser Thr Asp Phe Ser Ser

```
    370                 375                 380

Gln Lys Gly Val Lys Gly Leu Pro Leu Asn Ile Gln Val Asp Thr Tyr
385                 390                 395                 400

Ser Tyr Asn Asn Arg Ser Asn Lys Pro Val His Arg Ala Tyr Cys Gln
                405                 410                 415

Ile Lys Val Phe Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu
            420                 425                 430

Glu Arg Lys Gln Ser Lys Arg Lys Val Ser Asp Val Lys Val Pro Leu
        435                 440                 445

Leu Pro Ser His Lys Arg Met Asp Ile Thr Val Phe Lys Pro Phe Ile
    450                 455                 460

Asp Leu Asp Thr Gln Pro Val Leu Phe Ile Pro Asp Val His Phe Ala
465                 470                 475                 480

Asn Leu Gln Arg Gly Thr His Val Leu Pro Ile Ala Ser Glu Glu Leu
                485                 490                 495

Glu Gly Glu Gly Ser Val Leu Lys Arg Gly Pro Tyr Gly Thr Glu Asp
            500                 505                 510

Asp Phe Ala Val Pro Pro Ser Thr Lys Leu Ala Arg Ile Glu Glu Pro
        515                 520                 525

Lys Arg Val Leu Leu Tyr Val Arg Lys Glu Ser Glu Glu Val Phe Asp
    530                 535                 540

Ala Leu Met Leu Lys Thr Pro Ser Leu Lys Gly Leu Met Glu Ala Ile
545                 550                 555                 560

Ser Asp Lys Tyr Asp Val Pro His Asp Lys Ile Gly Lys Ile Phe Lys
                565                 570                 575

Lys Cys Lys Lys Gly Ile Leu Val Asn Met Asp Asp Asn Ile Val Lys
            580                 585                 590

His Tyr Ser Asn Glu Asp Thr Phe Gln Leu Gln Ile Glu Glu Ala Gly
        595                 600                 605

Gly Ser Tyr Lys Leu Thr Leu Thr Glu Ile
    610                 615
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<222> (67)..(1941)
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tcaaac atg tca caa gag tca gac aat aat aaa aga cta gtg gcc tta 108
Met Ser Gln Glu Ser Asp Asn Asn Lys Arg Leu Val Ala Leu
1 5 10

gtg ccc atg ccc agt gac cct cca ttc aat acc cga aga gcc tac acc 156
Val Pro Met Pro Ser Asp Pro Pro Phe Asn Thr Arg Arg Ala Tyr Thr
15 20 25 30

agt gag gat gaa gcc tgg aag tca tac ttg gag aat ccc ctg aca gca 204
Ser Glu Asp Glu Ala Trp Lys Ser Tyr Leu Glu Asn Pro Leu Thr Ala
35 40 45

gcc acc aag gcc atg atg agc att aat ggt gat gag gac agt gct gct 252
Ala Thr Lys Ala Met Met Ser Ile Asn Gly Asp Glu Asp Ser Ala Ala
50 55 60

gcc ctc ggc ctg ctc tat gac tac tac aag gtt cct cga gac aag agg 300
Ala Leu Gly Leu Leu Tyr Asp Tyr Tyr Lys Val Pro Arg Asp Lys Arg
65 70 75

ctg ctg tct gta agc aaa gca agt gac agc caa gaa gac cag gag aaa 348
Leu Leu Ser Val Ser Lys Ala Ser Asp Ser Gln Glu Asp Gln Glu Lys
80 85 90

aga aac tgc ctt ggc acc agt gaa gcc cag agt aat ttg agt gga gga 396
Arg Asn Cys Leu Gly Thr Ser Glu Ala Gln Ser Asn Leu Ser Gly Gly
95 100 105 110

gaa aac cga gtg caa gtc cta aag act gtt cca gtg aac ctt tcc cta 444
Glu Asn Arg Val Gln Val Leu Lys Thr Val Pro Val Asn Leu Ser Leu
115 120 125

aat caa gat cac ctg gag aat tcc aag cgg gaa cag tac agc atc agc 492
Asn Gln Asp His Leu Glu Asn Ser Lys Arg Glu Gln Tyr Ser Ile Ser
130 135 140

ttc ccc gag agc tct gcc atc atc ccg gtg tcg gga atc acg gtg gtg 540
Phe Pro Glu Ser Ser Ala Ile Ile Pro Val Ser Gly Ile Thr Val Val
145 150 155

aaa gct gaa gat ttc aca cca gtt ttc atg gcc cca cct gtg cac tat 588
Lys Ala Glu Asp Phe Thr Pro Val Phe Met Ala Pro Pro Val His Tyr
160 165 170

ccc cgg gga gat ggg gaa gag caa cga gtg gtt atc ttt gaa cag act 636
Pro Arg Gly Asp Gly Glu Glu Gln Arg Val Val Ile Phe Glu Gln Thr
175 180 185 190

cag tat gac gtg ccc tcg ctg gcc acc cac agc gcc tat ctc aaa gac 684
Gln Tyr Asp Val Pro Ser Leu Ala Thr His Ser Ala Tyr Leu Lys Asp
195 200 205

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gac cag cgc agc act ccg gac agc aca tac agc gag agc ttc aag gac      732
Asp Gln Arg Ser Thr Pro Asp Ser Thr Tyr Ser Glu Ser Phe Lys Asp
            210                 215                 220

gca gcc aca gag aaa ttt cgg agt gct tca gtt ggg gct gag gag tac      780
Ala Ala Thr Glu Lys Phe Arg Ser Ala Ser Val Gly Ala Glu Glu Tyr
        225                 230                 235

atg tat gat cag aca tca agt ggc aca ttt cag tac acc ctg gaa gcc      828
Met Tyr Asp Gln Thr Ser Ser Gly Thr Phe Gln Tyr Thr Leu Glu Ala
    240                 245                 250

acc aaa tct ctc cgt cag aag cag ggg gag ggc ccc atg acc tac ctc      876
Thr Lys Ser Leu Arg Gln Lys Gln Gly Glu Gly Pro Met Thr Tyr Leu
255                 260                 265                 270

aac aaa gga cag ttc tat gcc ata aca ctc agc gag acc gga gac aac      924
Asn Lys Gly Gln Phe Tyr Ala Ile Thr Leu Ser Glu Thr Gly Asp Asn
                275                 280                 285

aaa tgc ttc cga cac ccc atc agc aaa gtc agg agt gtg gtg atg gtg      972
Lys Cys Phe Arg His Pro Ile Ser Lys Val Arg Ser Val Val Met Val
            290                 295                 300

gtc ttc agt gaa gac aaa aac aga gat gaa cag ctc aaa tac tgg aaa     1020
Val Phe Ser Glu Asp Lys Asn Arg Asp Glu Gln Leu Lys Tyr Trp Lys
        305                 310                 315

tac tgg cac tct cgg cag cat acg gcg aag cag agg gtc ctt gac att     1068
Tyr Trp His Ser Arg Gln His Thr Ala Lys Gln Arg Val Leu Asp Ile
    320                 325                 330

gcc gat tac aag gag agc ttt aat acg att gga aac att gaa gag att     1116
Ala Asp Tyr Lys Glu Ser Phe Asn Thr Ile Gly Asn Ile Glu Glu Ile
335                 340                 345                 350

gca tat aat gct gtt tcc ttt acc tgg gac gtg aat gaa gag gcg aag     1164
Ala Tyr Asn Ala Val Ser Phe Thr Trp Asp Val Asn Glu Glu Ala Lys
                355                 360                 365

att ttc atc acc gtg aat tgc ttg agc aca gat ttc tcc tcc caa aaa     1212
Ile Phe Ile Thr Val Asn Cys Leu Ser Thr Asp Phe Ser Ser Gln Lys
            370                 375                 380

ggg gtg aaa gga ctt cct ttg atg att cag att gac aca tac agt tat     1260
Gly Val Lys Gly Leu Pro Leu Met Ile Gln Ile Asp Thr Tyr Ser Tyr
        385                 390                 395

aac aat cgt agc aat aaa ccc att cat aga gct tat tgc cag atc aag     1308
Asn Asn Arg Ser Asn Lys Pro Ile His Arg Ala Tyr Cys Gln Ile Lys
    400                 405                 410

gtc ttc tgt gac aaa gga gca gaa aga aaa atc cga gat gaa gag cgg     1356
Val Phe Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu Glu Arg
415                 420                 425                 430
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aag cag aac agg aag aaa ggg aaa ggc cag gcc tcc caa act caa tgc      1404
Lys Gln Asn Arg Lys Lys Gly Lys Gly Gln Ala Ser Gln Thr Gln Cys
                435                 440                 445

aac agc tcc tct gat ggg aag ttg gct gcc ata cct tta cag aag aag      1452
Asn Ser Ser Ser Asp Gly Lys Leu Ala Ala Ile Pro Leu Gln Lys Lys
            450                 455                 460

agt gac atc acc tac ttc aaa acc atg cct gat ctc cac tca cag cca      1500
Ser Asp Ile Thr Tyr Phe Lys Thr Met Pro Asp Leu His Ser Gln Pro
        465                 470                 475

gtt ctc ttc ata cct gat gtt cac ttt gca aac ctg cag agg acc gga      1548
Val Leu Phe Ile Pro Asp Val His Phe Ala Asn Leu Gln Arg Thr Gly
    480                 485                 490

cag gtg tat tac aac acg gat gat gaa cga gaa ggt ggc agt gtc ctt      1596
Gln Val Tyr Tyr Asn Thr Asp Asp Glu Arg Glu Gly Gly Ser Val Leu
495                 500                 505                 510

gtt aaa cgg atg ttc cgg ccc atg gaa gag gag ttt ggt cca gtg cct      1644
Val Lys Arg Met Phe Arg Pro Met Glu Glu Glu Phe Gly Pro Val Pro
                515                 520                 525

tca aag cag atg aaa gaa gaa ggg aca aag cga gtg ctc ttg tac gtg      1692
Ser Lys Gln Met Lys Glu Glu Gly Thr Lys Arg Val Leu Leu Tyr Val
            530                 535                 540

agg aag gag act gac gat gtg ttc gat gca ttg atg ttg aag tct ccc      1740
Arg Lys Glu Thr Asp Asp Val Phe Asp Ala Leu Met Leu Lys Ser Pro
        545                 550                 555

aca gtg aag ggc ctg atg gaa gcg ata tct gag aaa tat ggg ctg ccc      1788
Thr Val Lys Gly Leu Met Glu Ala Ile Ser Glu Lys Tyr Gly Leu Pro
    560                 565                 570

gtg gag aag ata gca aag ctt tac aag aaa agc aaa aaa ggc atc ttg      1836
Val Glu Lys Ile Ala Lys Leu Tyr Lys Lys Ser Lys Lys Gly Ile Leu
575                 580                 585                 590

gtg aac atg gat gac aac atc atc gag cac tac tcg aac gag gac acc      1884
Val Asn Met Asp Asp Asn Ile Ile Glu His Tyr Ser Asn Glu Asp Thr
                595                 600                 605

ttc atc ctc aac atg gag agc atg gtg gag ggc ttc aag gtc acg ctc      1932
Phe Ile Leu Asn Met Glu Ser Met Val Glu Gly Phe Lys Val Thr Leu
            610                 615                 620

atg gaa atc tagccctggg tttggcatcc gctttggctg gagctctcag             1981
Met Glu Ile
        625

tgcgttcctc cctgagagag acagaagccc cagccccaga acctggagac ccatctcccc   2041

catctcacaa ctgctgttac aagaccgtgc tggggagtgg ggcaagggac aggccccact   2101
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gtcggtgtgc ttggcccatc cactggcacc taccacggag ctgaagcctg agcccctcag 2161

gaaggtgcct taggcctgtt ggattcctat ttattgccca ccttttcctg gagcccaggt 2221

ccaggcccgc caggactctg caggtcactg ctagctccag atgagaccgt ccagcgttcc 2281

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gccactgttc tctttgaggg gacaggttta ggggtttgcg ttcgcccttg tgggctgaag 3481

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gacacaggca acctacccct ctctctccag cctctttatg aaactgtttg tttgccagtc 4141

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tcatggtggt gacaattgcc acaagggata tgaggccagt gccaccagag ggtggtgcca 4261

agtgccacat cccttccgat ccattccccc ctgcatcctc ggagcacccc agtttgcctt 4321

tgatgtgtcc gctgtgtatg ttagctgaac tttgatgagc aaaatttcct gagcgaaaca 4381

ctccaaagag ataggaaaac ttgccgcctc ttctttttg tcccttaatc aaactcaaat 4441

aagcttaaaa aaaatccatg gaagatcatg gacatgtgaa atgagcattt ttttcttttt 4501

ttttttttt tttaacaaag tctgaactga g 4532

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<212> PRT
<213> human

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Met Ser Gln Glu Ser Asp Asn Asn Lys Arg Leu Val Ala Leu Val Pro
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Met Pro Ser Asp Pro Pro Phe Asn Thr Arg Arg Ala Tyr Thr Ser Glu
20 25 30

Asp Glu Ala Trp Lys Ser Tyr Leu Glu Asn Pro Leu Thr Ala Ala Thr
35 40 45

Lys Ala Met Met Ser Ile Asn Gly Asp Glu Asp Ser Ala Ala Ala Leu
50 55 60

Gly Leu Leu Tyr Asp Tyr Tyr Lys Val Pro Arg Asp Lys Arg Leu Leu
65 70 75 80

Ser Val Ser Lys Ala Ser Asp Ser Gln Glu Asp Gln Glu Lys Arg Asn
85 90 95

Cys Leu Gly Thr Ser Glu Ala Gln Ser Asn Leu Ser Gly Gly Glu Asn
100 105 110

Arg Val Gln Val Leu Lys Thr Val Pro Val Asn Leu Ser Leu Asn Gln
115 120 125

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Asp His Leu Glu Asn Ser Lys Arg Glu Gln Tyr Ser Ile Ser Phe Pro
    130                 135                 140

Glu Ser Ser Ala Ile Ile Pro Val Ser Gly Ile Thr Val Val Lys Ala
145                 150                 155                 160

Glu Asp Phe Thr Pro Val Phe Met Ala Pro Pro Val His Tyr Pro Arg
                165                 170                 175

Gly Asp Gly Glu Glu Gln Arg Val Val Ile Phe Glu Gln Thr Gln Tyr
            180                 185                 190

Asp Val Pro Ser Leu Ala Thr His Ser Ala Tyr Leu Lys Asp Asp Gln
        195                 200                 205

Arg Ser Thr Pro Asp Ser Thr Tyr Ser Glu Ser Phe Lys Asp Ala Ala
    210                 215                 220

Thr Glu Lys Phe Arg Ser Ala Ser Val Gly Ala Glu Glu Tyr Met Tyr
225                 230                 235                 240

Asp Gln Thr Ser Ser Gly Thr Phe Gln Tyr Thr Leu Glu Ala Thr Lys
                245                 250                 255

Ser Leu Arg Gln Lys Gln Gly Glu Gly Pro Met Thr Tyr Leu Asn Lys
            260                 265                 270

Gly Gln Phe Tyr Ala Ile Thr Leu Ser Glu Thr Gly Asp Asn Lys Cys
        275                 280                 285

Phe Arg His Pro Ile Ser Lys Val Arg Ser Val Val Met Val Val Phe
    290                 295                 300

Ser Glu Asp Lys Asn Arg Asp Glu Gln Leu Lys Tyr Trp Lys Tyr Trp
305                 310                 315                 320

His Ser Arg Gln His Thr Ala Lys Gln Arg Val Leu Asp Ile Ala Asp
                325                 330                 335

Tyr Lys Glu Ser Phe Asn Thr Ile Gly Asn Ile Glu Glu Ile Ala Tyr
            340                 345                 350

Asn Ala Val Ser Phe Thr Trp Asp Val Asn Glu Glu Ala Lys Ile Phe
        355                 360                 365

Ile Thr Val Asn Cys Leu Ser Thr Asp Phe Ser Ser Gln Lys Gly Val
    370                 375                 380

Lys Gly Leu Pro Leu Met Ile Gln Ile Asp Thr Tyr Ser Tyr Asn Asn
385                 390                 395                 400

Arg Ser Asn Lys Pro Ile His Arg Ala Tyr Cys Gln Ile Lys Val Phe
                405                 410                 415

Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu Glu Arg Lys Gln
            420                 425                 430
```

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Asn Arg Lys Lys Gly Lys Gly Gln Ala Ser Gln Thr Gln Cys Asn Ser
        435                 440                 445

Ser Ser Asp Gly Lys Leu Ala Ala Ile Pro Leu Gln Lys Lys Ser Asp
    450                 455                 460

Ile Thr Tyr Phe Lys Thr Met Pro Asp Leu His Ser Gln Pro Val Leu
465                 470                 475                 480

Phe Ile Pro Asp Val His Phe Ala Asn Leu Gln Arg Thr Gly Gln Val
                485                 490                 495

Tyr Tyr Asn Thr Asp Asp Glu Arg Glu Gly Gly Ser Val Leu Val Lys
            500                 505                 510

Arg Met Phe Arg Pro Met Glu Glu Glu Phe Gly Pro Val Pro Ser Lys
        515                 520                 525

Gln Met Lys Glu Glu Gly Thr Lys Arg Val Leu Leu Tyr Val Arg Lys
    530                 535                 540

Glu Thr Asp Asp Val Phe Asp Ala Leu Met Leu Lys Ser Pro Thr Val
545                 550                 555                 560

Lys Gly Leu Met Glu Ala Ile Ser Glu Lys Tyr Gly Leu Pro Val Glu
                565                 570                 575

Lys Ile Ala Lys Leu Tyr Lys Lys Ser Lys Lys Gly Ile Leu Val Asn
            580                 585                 590

Met Asp Asp Asn Ile Ile Glu His Tyr Ser Asn Glu Asp Thr Phe Ile
        595                 600                 605

Leu Asn Met Glu Ser Met Val Glu Gly Phe Lys Val Thr Leu Met Glu
    610                 615                 620

Ile
625

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                                                    Met Trp Met
                                                    1

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```
Asn Ser Ile Leu Pro Ile Phe Leu Phe Arg Ser Val Arg Leu Leu Lys
    5                   10                  15

aac gac cca gtc aac ttg cag aaa ttc tct tac act agt gag gat gag      151
Asn Asp Pro Val Asn Leu Gln Lys Phe Ser Tyr Thr Ser Glu Asp Glu
20                  25                  30                  35

gcc tgg aag acg tac cta gaa aac ccg ttg aca gct gcc aca aag gcc      199
Ala Trp Lys Thr Tyr Leu Glu Asn Pro Leu Thr Ala Ala Thr Lys Ala
                40                  45                  50

atg atg aga gtc aat gga gat gat gac agt gtt gcg gcc ttg agc ttc      247
Met Met Arg Val Asn Gly Asp Asp Asp Ser Val Ala Ala Leu Ser Phe
            55                  60                  65

ctc tat gat tac tac atg ggt ccc aag gag aag cgg ata ttg tcc tcc      295
Leu Tyr Asp Tyr Tyr Met Gly Pro Lys Glu Lys Arg Ile Leu Ser Ser
        70                  75                  80

agc act ggg ggc agg aat gac caa gga aag agg tac tac cat ggc atg      343
Ser Thr Gly Gly Arg Asn Asp Gln Gly Lys Arg Tyr Tyr His Gly Met
    85                  90                  95

gaa tat gag acg gac ctc act ccc ctt gaa agc ccc aca cac ctc atg      391
Glu Tyr Glu Thr Asp Leu Thr Pro Leu Glu Ser Pro Thr His Leu Met
100                 105                 110                 115

aaa ytc ctg aca gag aac gtg tct gga acc cca gag tac cca gat ttg      439
Lys Xaa Leu Thr Glu Asn Val Ser Gly Thr Pro Glu Tyr Pro Asp Leu
                120                 125                 130

ctc aag aag aat aac ctg atg agc ttg gag ggg gcc ttg ccc acc cct      487
Leu Lys Lys Asn Asn Leu Met Ser Leu Glu Gly Ala Leu Pro Thr Pro
            135                 140                 145

ggc aag gca gct ccc ctc cct gca ggc ccc agc aag ctg gag gcc ggc      535
Gly Lys Ala Ala Pro Leu Pro Ala Gly Pro Ser Lys Leu Glu Ala Gly
        150                 155                 160

tct gtg gac agc tac ctg tta ccc acy act gat atg tat gat aat ggc      583
Ser Val Asp Ser Tyr Leu Leu Pro Xaa Thr Asp Met Tyr Asp Asn Gly
    165                 170                 175

tcc ctc aac tcc ttg ttt gag agc att cat ggg gtg ccg ccc aca cag      631
Ser Leu Asn Ser Leu Phe Glu Ser Ile His Gly Val Pro Pro Thr Gln
180                 185                 190                 195

cgc tgg cag cca gac agc acc ttc aaa gat gac cca cag gag tcg atg      679
Arg Trp Gln Pro Asp Ser Thr Phe Lys Asp Asp Pro Gln Glu Ser Met
                200                 205                 210

ctc ttc cca gat atc ctg aaa acc tcc ccg gaa ccc cca tgt cca gag      727
Leu Phe Pro Asp Ile Leu Lys Thr Ser Pro Glu Pro Pro Cys Pro Glu
            215                 220                 225

gac tac ccc agc ctc aaa agt gac ttt gaa tac acc ctg ggc tcc ccc      775
```

```
Asp Tyr Pro Ser Leu Lys Ser Asp Phe Glu Tyr Thr Leu Gly Ser Pro
        230                 235                 240

aaa gcc atc cac atc aag tca ggc gag tca ccc atg gcc tac ctc aac      823
Lys Ala Ile His Ile Lys Ser Gly Glu Ser Pro Met Ala Tyr Leu Asn
    245                 250                 255

aaa ggc cag ttc tac ccc gtc acc ctg cgg acc cca gca ggt ggc aaa      871
Lys Gly Gln Phe Tyr Pro Val Thr Leu Arg Thr Pro Ala Gly Gly Lys
260                 265                 270                 275

ggc ctt gcc ttg tcc tcc aac aaa gtc aag agt gtg gtg atg gtt gtc      919
Gly Leu Ala Leu Ser Ser Asn Lys Val Lys Ser Val Val Met Val Val
                280                 285                 290

ttc gac aat gag aag gtc cca gta gag cag ctg cgc ttc tgg aag cac      967
Phe Asp Asn Glu Lys Val Pro Val Glu Gln Leu Arg Phe Trp Lys His
            295                 300                 305

tgg cat tcc cgg caa ccc act gcc aag cag cgg gtc att gac gtg gct     1015
Trp His Ser Arg Gln Pro Thr Ala Lys Gln Arg Val Ile Asp Val Ala
        310                 315                 320

gac tgc aaa gaa aac ttc aac act gtg gag cac att gag gag gtg gcc     1063
Asp Cys Lys Glu Asn Phe Asn Thr Val Glu His Ile Glu Glu Val Ala
    325                 330                 335

tat aat gca ctg tcc ttt gtg tgg aac gtg aat gaa gag gcc aag gtg     1111
Tyr Asn Ala Leu Ser Phe Val Trp Asn Val Asn Glu Glu Ala Lys Val
340                 345                 350                 355

ttc atc ggc gta aac tgt ctg agc aca gac ttt tcc tca caa aag ggg     1159
Phe Ile Gly Val Asn Cys Leu Ser Thr Asp Phe Ser Ser Gln Lys Gly
                360                 365                 370

gtg aag ggt gtc ccc ctg aac ctg cag att gac acc tat gac tgt ggc     1207
Val Lys Gly Val Pro Leu Asn Leu Gln Ile Asp Thr Tyr Asp Cys Gly
            375                 380                 385

ttg ggc act gag cgc ctg gta cac cgt gct gtc tgc cag atc aag atc     1255
Leu Gly Thr Glu Arg Leu Val His Arg Ala Val Cys Gln Ile Lys Ile
        390                 395                 400

ttc tgt gac aag gga gct gag agg aag atg cgc gat gac gag cgg aag     1303
Phe Cys Asp Lys Gly Ala Glu Arg Lys Met Arg Asp Asp Glu Arg Lys
    405                 410                 415

cag ttc cgg agg aag gtc aag tgc cct gac tcc agc aac agt ggc gtc     1351
Gln Phe Arg Arg Lys Val Lys Cys Pro Asp Ser Ser Asn Ser Gly Val
420                 425                 430                 435

aag ggc tgc ctg ctg tcg ggc ttc agg ggc aat gag acg acc tac ctt     1399
Lys Gly Cys Leu Leu Ser Gly Phe Arg Gly Asn Glu Thr Thr Tyr Leu
                440                 445                 450

cgg cca gag act gac ctg gag acg cca ccc gtg ctg ttc atc ccc aat     1447
```

```
Arg Pro Glu Thr Asp Leu Glu Thr Pro Pro Val Leu Phe Ile Pro Asn
            455                 460                 465

gtg cac ttc tcc agc ctg cag cgc tct gga ggg gca gcc ccc tcg gca     1495
Val His Phe Ser Ser Leu Gln Arg Ser Gly Gly Ala Ala Pro Ser Ala
        470                 475                 480

gga ccc agc agc tcc aac agg ctg cct ctg aag cgt acc tgc tcg ccc     1543
Gly Pro Ser Ser Ser Asn Arg Leu Pro Leu Lys Arg Thr Cys Ser Pro
    485                 490                 495

ttc act gag gag ttt gag cct ctg ccc tcc aag cag gcc aag gaa ggc     1591
Phe Thr Glu Glu Phe Glu Pro Leu Pro Ser Lys Gln Ala Lys Glu Gly
500                 505                 510                 515

gac ctt cag aga gtt ctg ctg tat gtg cgg agg gag act gag gag gtg     1639
Asp Leu Gln Arg Val Leu Leu Tyr Val Arg Arg Glu Thr Glu Glu Val
                520                 525                 530

ttt gac gcg ctc atg ttg aag acc cca gac ctg aag ggg ctg agg aat     1687
Phe Asp Ala Leu Met Leu Lys Thr Pro Asp Leu Lys Gly Leu Arg Asn
            535                 540                 545

gcg atc tct gag aag tat ggg ttc cct gaa gag aac att tac aaa gtc     1735
Ala Ile Ser Glu Lys Tyr Gly Phe Pro Glu Glu Asn Ile Tyr Lys Val
        550                 555                 560

tac aag aaa tgc aag cga gga atc tta gtc aac atg gac aac aac atc     1783
Tyr Lys Lys Cys Lys Arg Gly Ile Leu Val Asn Met Asp Asn Asn Ile
    565                 570                 575

att cag cat tac agc aac cac gtc gcc ttc ctg ctg gac atg ggg gag     1831
Ile Gln His Tyr Ser Asn His Val Ala Phe Leu Leu Asp Met Gly Glu
580                 585                 590                 595

ctg gac ggc aaa att cag atc atc ctt aag gag ctg taa                 1870
Leu Asp Gly Lys Ile Gln Ile Ile Leu Lys Glu Leu
                600                 605
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<210> 8
<211> 607
<212> PRT
<213> human

<220>
<221> misc_feature
<222> (117)..(117)
<223> The 'Xaa' at location 117 stands for Leu, or Phe.

<220>
<221> misc_feature
<222> (172)..(172)
<223> The 'Xaa' at location 172 stands for Thr.

<400> 8
Met Trp Met Asn Ser Ile Leu Pro Ile Phe Leu Phe Arg Ser Val Arg

```
1               5                   10                  15

Leu Leu Lys Asn Asp Pro Val Asn Leu Gln Lys Phe Ser Tyr Thr Ser
            20                  25                  30

Glu Asp Glu Ala Trp Lys Thr Tyr Leu Glu Asn Pro Leu Thr Ala Ala
        35                  40                  45

Thr Lys Ala Met Met Arg Val Asn Gly Asp Asp Asp Ser Val Ala Ala
    50                  55                  60

Leu Ser Phe Leu Tyr Asp Tyr Tyr Met Gly Pro Lys Glu Lys Arg Ile
65                  70                  75                  80

Leu Ser Ser Ser Thr Gly Gly Arg Asn Asp Gln Gly Lys Arg Tyr Tyr
                85                  90                  95

His Gly Met Glu Tyr Glu Thr Asp Leu Thr Pro Leu Glu Ser Pro Thr
            100                 105                 110

His Leu Met Lys Xaa Leu Thr Glu Asn Val Ser Gly Thr Pro Glu Tyr
        115                 120                 125

Pro Asp Leu Leu Lys Lys Asn Asn Leu Met Ser Leu Glu Gly Ala Leu
    130                 135                 140

Pro Thr Pro Gly Lys Ala Ala Pro Leu Pro Ala Gly Pro Ser Lys Leu
145                 150                 155                 160

Glu Ala Gly Ser Val Asp Ser Tyr Leu Leu Pro Xaa Thr Asp Met Tyr
                165                 170                 175

Asp Asn Gly Ser Leu Asn Ser Leu Phe Glu Ser Ile His Gly Val Pro
            180                 185                 190

Pro Thr Gln Arg Trp Gln Pro Asp Ser Thr Phe Lys Asp Asp Pro Gln
        195                 200                 205

Glu Ser Met Leu Phe Pro Asp Ile Leu Lys Thr Ser Pro Glu Pro Pro
    210                 215                 220

Cys Pro Glu Asp Tyr Pro Ser Leu Lys Ser Asp Phe Glu Tyr Thr Leu
225                 230                 235                 240

Gly Ser Pro Lys Ala Ile His Ile Lys Ser Gly Glu Ser Pro Met Ala
                245                 250                 255

Tyr Leu Asn Lys Gly Gln Phe Tyr Pro Val Thr Leu Arg Thr Pro Ala
            260                 265                 270

Gly Gly Lys Gly Leu Ala Leu Ser Ser Asn Lys Val Lys Ser Val Val
        275                 280                 285

Met Val Val Phe Asp Asn Glu Lys Val Pro Val Glu Gln Leu Arg Phe
    290                 295                 300
```

```
Trp Lys His Trp His Ser Arg Gln Pro Thr Ala Lys Gln Arg Val Ile
305                 310                 315                 320

Asp Val Ala Asp Cys Lys Glu Asn Phe Asn Thr Val Glu His Ile Glu
                325                 330                 335

Glu Val Ala Tyr Asn Ala Leu Ser Phe Val Trp Asn Val Asn Glu Glu
            340                 345                 350

Ala Lys Val Phe Ile Gly Val Asn Cys Leu Ser Thr Asp Phe Ser Ser
        355                 360                 365

Gln Lys Gly Val Lys Gly Val Pro Leu Asn Leu Gln Ile Asp Thr Tyr
    370                 375                 380

Asp Cys Gly Leu Gly Thr Glu Arg Leu Val His Arg Ala Val Cys Gln
385                 390                 395                 400

Ile Lys Ile Phe Cys Asp Lys Gly Ala Glu Arg Lys Met Arg Asp Asp
                405                 410                 415

Glu Arg Lys Gln Phe Arg Arg Lys Val Lys Cys Pro Asp Ser Ser Asn
            420                 425                 430

Ser Gly Val Lys Gly Cys Leu Leu Ser Gly Phe Arg Gly Asn Glu Thr
        435                 440                 445

Thr Tyr Leu Arg Pro Glu Thr Asp Leu Glu Thr Pro Pro Val Leu Phe
    450                 455                 460

Ile Pro Asn Val His Phe Ser Ser Leu Gln Arg Ser Gly Gly Ala Ala
465                 470                 475                 480

Pro Ser Ala Gly Pro Ser Ser Ser Asn Arg Leu Pro Leu Lys Arg Thr
                485                 490                 495

Cys Ser Pro Phe Thr Glu Glu Phe Glu Pro Leu Pro Ser Lys Gln Ala
            500                 505                 510

Lys Glu Gly Asp Leu Gln Arg Val Leu Leu Tyr Val Arg Arg Glu Thr
        515                 520                 525

Glu Glu Val Phe Asp Ala Leu Met Leu Lys Thr Pro Asp Leu Lys Gly
    530                 535                 540

Leu Arg Asn Ala Ile Ser Glu Lys Tyr Gly Phe Pro Glu Glu Asn Ile
545                 550                 555                 560

Tyr Lys Val Tyr Lys Lys Cys Lys Arg Gly Ile Leu Val Asn Met Asp
                565                 570                 575

Asn Asn Ile Ile Gln His Tyr Ser Asn His Val Ala Phe Leu Leu Asp
            580                 585                 590

Met Gly Glu Leu Asp Gly Lys Ile Gln Ile Ile Leu Lys Glu Leu
        595                 600                 605
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<210> 9
<211> 3113
<212> DNA
<213> murine

<220>
<221> misc_feature
<222> (2634)..(2634)
<223> n = any nucleotide

<220>
<221> misc_feature
<222> (2968)..(2968)
<223> n = any nucleotide

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ctaaacagca taccaaatgt gacggagcag cccctcattt ctgctggaga aaacagggta 120

caagtgctga aaaacgtgcc cttcaacatc gtcctccccc atagcaacca gctgggcatt 180

gataagagag gccatctgac agctcccgat acaacagtca ctgtctccat agcgaccatg 240

cctacccact ccatcaagac agaaatccag ccgcacggct ttgctgtggg aatccctcca 300

gccgtgtacc actctgagcc caccgaacgc gtggtggttt ttgaccggag cctcagcact 360

gatcagttca gctctggcac tcagcccccc aatgctcagc ggaggactcc agactccacc 420

ttctccgaga ccttcaagga gggcgttcag gaggttttct tcccctcgga actcagcctt 480

cggatgccgg gcatgaattc agaggactat gtctttgaca atgtttctgg gaacaacttt 540

gagtataccc tggaagcctc caagtcactg cggcagaagc aaggggacag cactatgaca 600

tacctgaata aaggccagtt ctatcctgtc accttaaagg aaggaagcag caatgaaggg 660

attcaccacc ctatcagcaa agttcgaagt gtgatcatgg tggtttttgc tgaagacaaa 720

agcagagaag accagctgag acactggaag tactggcact cccgtcagca cacggccaaa 780

cagaggtgca ttgacattgc tgactacaaa gaaagtttca acactatcag caacattgag 840

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atctctgtga actgcttgag cacagatttc tcttctcaga agggtgtgaa gggcttgcca 960

ctcaacattc aaatcgacac atacagctat aacaaccgca gcaacaagcc ggttcaccgg 1020

gcctactgcc agataaaggt cttctgcgac aagggagctg aaaggaaaat tcgggatgaa 1080

gaacgaaaac agagcaagag aaaagtgtct gacgttaaag tgcagctgct tccctcacac 1140

aaacggacag acatcacagt gttcaagccc ttcctggacc tcgacactca gcctgtcctc 1200

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tctgaagaac tggaaggtga aggctctgtc ttgaaaagag ggccattcgg aaccgaagat 1320

gactttggag ttcctcctcc tgctaagctg actcggacag aagaacccaa gagagtgctg 1380

ctctatgtcc gaaaggaatc agaagaagtc ttcgacgccc tgatgctcaa gacgccgtct 1440

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aaaatattta agaagtgcaa aaaagggatc ctcgtgaaca tggacgacaa cattgtgaag 1560

cactactcca atgaggacac cttccagctg cagatagagg aagccggcgg ctcgtacaag 1620

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gcgagagagg ggaaggcagt agcttgtctt tgaggctttt gtgttctcgc ctgacctcag 2040

tctaactctg actgccttga ggagtgggcc cagccctcag caataaaggg ctaagccttc 2100

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aacttccctt ggacatgtgg actgcctttc tgatgaagaa cttgcgtgag tgacagtgtg 2220

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taggtcattt gtatgagtag gattgttagc ggtatacgta rgttaaaaag tactctaatg 2940

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tttctatttt gttttatgaa atcagcttta cttgttttaa ttgtatcatt gaacatgtgt 3060

tttaaaccaa agggattgaa ttttatatgt ctatttcaaa aaaaaaaaaa aaa 3113

<210> 10
<211> 536
<212> PRT
<213> murine

<400> 10

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Met Ala Ser Leu Asp Asp Glu Leu Cys Asp Leu Asn Ser Ile Pro Asn
1               5                  10                  15

Val Thr Glu Gln Pro Leu Ile Ser Ala Gly Glu Asn Arg Val Gln Val
            20                  25                  30

Leu Lys Asn Val Pro Phe Asn Ile Val Leu Pro His Ser Asn Gln Leu
        35                  40                  45

Gly Ile Asp Lys Arg Gly His Leu Thr Ala Pro Asp Thr Thr Val Thr
    50                  55                  60

Val Ser Ile Ala Thr Met Pro Thr His Ser Ile Lys Thr Glu Ile Gln
65                  70                  75                  80

Pro His Gly Phe Ala Val Gly Ile Pro Pro Ala Val Tyr His Ser Glu
                85                  90                  95

Pro Thr Glu Arg Val Val Val Phe Asp Arg Ser Leu Ser Thr Asp Gln
            100                 105                 110

Phe Ser Ser Gly Thr Gln Pro Pro Asn Ala Gln Arg Arg Thr Pro Asp
        115                 120                 125

Ser Thr Phe Ser Glu Thr Phe Lys Glu Gly Val Gln Glu Val Phe Phe
    130                 135                 140

Pro Ser Glu Leu Ser Leu Arg Met Pro Gly Met Asn Ser Glu Asp Tyr
145                 150                 155                 160

Val Phe Asp Asn Val Ser Gly Asn Asn Phe Glu Tyr Thr Leu Glu Ala
                165                 170                 175

Ser Lys Ser Leu Arg Gln Lys Gln Gly Asp Ser Thr Met Thr Tyr Leu
            180                 185                 190

Asn Lys Gly Gln Phe Tyr Pro Val Thr Leu Lys Glu Gly Ser Ser Asn
        195                 200                 205
```

```
Glu Gly Ile His His Pro Ile Ser Lys Val Arg Ser Val Ile Met Val
    210                 215                 220

Val Phe Ala Glu Asp Lys Ser Arg Glu Asp Gln Leu Arg His Trp Lys
225                 230                 235                 240

Tyr Trp His Ser Arg Gln His Thr Ala Lys Gln Arg Cys Ile Asp Ile
                245                 250                 255

Ala Asp Tyr Lys Glu Ser Phe Asn Thr Ile Ser Asn Ile Glu Glu Ile
            260                 265                 270

Ala Tyr Asn Ala Ile Ser Phe Thr Trp Asp Ile Asn Asp Glu Ala Lys
        275                 280                 285

Val Phe Ile Ser Val Asn Cys Leu Ser Thr Asp Phe Ser Ser Gln Lys
    290                 295                 300

Gly Val Lys Gly Leu Pro Leu Asn Ile Gln Ile Asp Thr Tyr Ser Tyr
305                 310                 315                 320

Asn Asn Arg Ser Asn Lys Pro Val His Arg Ala Tyr Cys Gln Ile Lys
                325                 330                 335

Val Phe Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu Glu Arg
            340                 345                 350

Lys Gln Ser Lys Arg Lys Val Ser Asp Val Lys Val Gln Leu Leu Pro
        355                 360                 365

Ser His Lys Arg Thr Asp Ile Thr Val Phe Lys Pro Phe Leu Asp Leu
    370                 375                 380

Asp Thr Gln Pro Val Leu Phe Ile Pro Asp Val His Phe Thr Asn Leu
385                 390                 395                 400

Gln Arg Gly Ser His Val Leu Ser Leu Pro Ser Glu Glu Leu Glu Gly
                405                 410                 415

Glu Gly Ser Val Leu Lys Arg Gly Pro Phe Gly Thr Glu Asp Asp Phe
            420                 425                 430

Gly Val Pro Pro Pro Ala Lys Leu Thr Arg Thr Glu Glu Pro Lys Arg
        435                 440                 445

Val Leu Leu Tyr Val Arg Lys Glu Ser Glu Glu Val Phe Asp Ala Leu
    450                 455                 460

Met Leu Lys Thr Pro Ser Leu Lys Gly Leu Met Glu Ala Ile Ser Asp
465                 470                 475                 480

Lys Tyr Asp Val Pro His Asp Lys Ile Gly Lys Ile Phe Lys Lys Cys
                485                 490                 495

Lys Lys Gly Ile Leu Val Asn Met Asp Asp Asn Ile Val Lys His Tyr
            500                 505                 510
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Ser Asn Glu Asp Thr Phe Gln Leu Gln Ile Glu Glu Ala Gly Gly Ser
515 520 525

Tyr Lys Leu Thr Leu Thr Glu Ile
530 535

<210> 11
<211> 3452
<212> DNA
<213> murine

<220>
<221> misc_feature
<222> (2973)..(2973)
<223> n = any nucleotide

<220>
<221> misc_feature
<222> (3307)..(3307)
<223> n = any nucleotide

<400> 11
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atcgggtgta ctgtcccaac ccgaaagtcc agttctgcgg cccggcagcg gcgagcgagc 120

gcgatgacac aggagtacga caacaaaagg cccgtgctgg tacttcagaa tgaagccctc 180

tacccacagc ggcgctccta taccagtgag gatgaagcct ggaagtcgtt cctggaaaac 240

cctctcactg cggcaaccaa agcgatgatg agcatcaacg gagacgaaga cagcgcggct 300

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ttcaacatcg tcctcccccа tagcaaccag ctgggcattg ataagagagg ccatctgaca 540

gctcccgata caacagtcac tgtctccata gcgaccatgc ctacccactc catcaagaca 600

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tttatatgtc tatttcaaaa aaaaaaaaaa aa 3452

<210> 12
<211> 618
<212> PRT
<213> murine

<400> 12

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20 25 30

Trp Lys Ser Phe Leu Glu Asn Pro Leu Thr Ala Ala Thr Lys Ala Met
35 40 45

Met Ser Ile Asn Gly Asp Glu Asp Ser Ala Ala Ala Leu Gly Leu Leu
50 55 60

Tyr Asp Tyr Tyr Lys Val Pro Arg Glu Arg Arg Ser Ser Ala Val Lys
65 70 75 80

Pro Glu Gly Glu His Pro Glu Pro Glu His Ser Lys Arg Asn Ser Ile
85 90 95

Pro Asn Val Thr Glu Gln Pro Leu Ile Ser Ala Gly Glu Asn Arg Val
100 105 110

Gln Val Leu Lys Asn Val Pro Phe Asn Ile Val Leu Pro His Ser Asn
115 120 125

Gln Leu Gly Ile Asp Lys Arg Gly His Leu Thr Ala Pro Asp Thr Thr
130 135 140

Val Thr Val Ser Ile Ala Thr Met Pro Thr His Ser Ile Lys Thr Glu
145 150 155 160

Ile Gln Pro His Gly Phe Ala Val Gly Ile Pro Pro Ala Val Tyr His
165 170 175

Ser Glu Pro Thr Glu Arg Val Val Val Phe Asp Arg Ser Leu Ser Thr
180 185 190

Asp Gln Phe Ser Ser Gly Thr Gln Pro Pro Asn Ala Gln Arg Arg Thr
195 200 205

Pro Asp Ser Thr Phe Ser Glu Thr Phe Lys Glu Gly Val Gln Glu Val
210 215 220

Phe Phe Pro Ser Glu Leu Ser Leu Arg Met Pro Gly Met Asn Ser Glu
225 230 235 240

Asp Tyr Val Phe Asp Asn Val Ser Gly Asn Asn Phe Glu Tyr Thr Leu
245 250 255

Glu Ala Ser Lys Ser Leu Arg Gln Lys Gln Gly Asp Ser Thr Met Thr
260 265 270

Tyr Leu Asn Lys Gly Gln Phe Tyr Pro Val Thr Leu Lys Glu Gly Ser
275 280 285

Ser Asn Glu Gly Ile His His Pro Ile Ser Lys Val Arg Ser Val Ile
290 295 300

Met Val Val Phe Ala Glu Asp Lys Ser Arg Glu Asp Gln Leu Arg His
305 310 315 320

Trp Lys Tyr Trp His Ser Arg Gln His Thr Ala Lys Gln Arg Cys Ile
325 330 335

Asp Ile Ala Asp Tyr Lys Glu Ser Phe Asn Thr Ile Ser Asn Ile Glu
340 345 350

Glu Ile Ala Tyr Asn Ala Ile Ser Phe Thr Trp Asp Ile Asn Asp Glu
355 360 365

Ala Lys Val Phe Ile Ser Val Asn Cys Leu Ser Thr Asp Phe Ser Ser
370 375 380

Gln Lys Gly Val Lys Gly Leu Pro Leu Asn Ile Gln Ile Asp Thr Tyr
385 390 395 400

Ser Tyr Asn Asn Arg Ser Asn Lys Pro Val His Arg Ala Tyr Cys Gln
405 410 415

Ile Lys Val Phe Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu

420 425 430

Glu Arg Lys Gln Ser Lys Arg Lys Val Ser Asp Val Lys Val Gln Leu
435 440 445

Leu Pro Ser His Lys Arg Thr Asp Ile Thr Val Phe Lys Pro Phe Leu
450 455 460

Asp Leu Asp Thr Gln Pro Val Leu Phe Ile Pro Asp Val His Phe Thr
465 470 475 480

Asn Leu Gln Arg Gly Ser His Val Leu Ser Leu Pro Ser Glu Glu Leu
485 490 495

Glu Gly Glu Gly Ser Val Leu Lys Arg Gly Pro Phe Gly Thr Glu Asp
500 505 510

Asp Phe Gly Val Pro Pro Pro Ala Lys Leu Thr Arg Thr Glu Glu Pro
515 520 525

Lys Arg Val Leu Leu Tyr Val Arg Lys Glu Ser Glu Glu Val Phe Asp
530 535 540

Ala Leu Met Leu Lys Thr Pro Ser Leu Lys Gly Leu Met Glu Ala Ile
545 550 555 560

Ser Asp Lys Tyr Asp Val Pro His Asp Lys Ile Gly Lys Ile Phe Lys
565 570 575

Lys Cys Lys Lys Gly Ile Leu Val Asn Met Asp Asp Asn Ile Val Lys
580 585 590

His Tyr Ser Asn Glu Asp Thr Phe Gln Leu Gln Ile Glu Glu Ala Gly
595 600 605

Gly Ser Tyr Lys Leu Thr Leu Thr Glu Ile
610 615

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gccttagtgc ccatgcccag tgaccctccc ttcaacaccc gaagagccta cacaagtgag 180

gatgaggcct ggaagtcata tctggagaac cccctgactg cggccaccaa ggcgatgatg 240

agcatcaacg gggacgagga cagtgctgcc gccctgggcc tgctctatga ctactacaag 300

gttcctcgag acaagagact tctgtctgtg agcaaagcaa gtgacagcca agaagaccag 360

gataaaagaa actgccttgg caccagtgaa gcccagatca atttgagcgg aggcgagaac 420

agagtgcagg ttctgaagac tgtcccggtg aacctctgtc taagtcaaga ccacatggag 480

aattcgaagc gcgagcagta cagtgtatcc atcaccgaga gctctgccgt catccccgtg 540

tcaggcatca ccgtggtgaa agccgaggat ttcacaccgg tgttcatggc gcccccggtg 600

cactatcccc gcgcggacag tgaggagcag cgcgtggtta tctttgaaca gactcagtac 660

gacctgccct ccatagccag ccacagctcc tatctcaagg acgaccagcg cagcacgccg 720

gacagcacct acagcgagag ctttaaggac ggcgcctcgg agaaatttcg gagtacttct 780

gttggtgctg acgagtatac atatgaccag acgggaagtg gtacatttca gtacaccctg 840

gaagccacca aatctctccg tcagaaacag ggggagggcc ccatgaccta cctcaacaaa 900

ggacaattct atgccataac actcagtgag actggagaca acaaatgctt ccgacacccc 960

atcagcaaag tcaggagtgt ggtgatggtg gtctttagtg aagacaaaaa ccgagatgag 1020

cagctgaaat actggaagta ctggcactcc cggcagcaca ctgccaagca gagggtcctt 1080

gacattgctg attacaagga gagcttcaac accatcggga acattgaaga gatcgcatac 1140

aatgctgttt ccttcacctg ggatgtgaac gaggaggcaa agatttttat caccgtgaat 1200

tgcctgagta cagatttctc ctcccaaaag ggtgtaaaag gacttcccct gatgattcag 1260

atcgacacgt acagctacaa caaccgcagc aataaaccca tccacagagc atactgccag 1320

atcaaggtct tctgtgacaa gggagcagaa agaaaaatcc gggatgaaga gagaaagcag 1380

aacaggaaga aagggaaggg ccaggcctct caagcccagt gcaacaactc ctctgatggg 1440

aagatggccg ccataccgtt acagaagaag agtgacatca cgtacttcaa aaccatgccc 1500

gacctgcact cacagcctgt gctcttcata ccagatgttc actttgcaaa cctacagagg 1560

accggacagg tttattacaa cacagacgat gagcgagaag gcagcagcgt ccttgttaag 1620

cggatgttca ggcccatgga agaggagttt ggtccaacac cgtctaagca gatcaaagaa 1680

gaaaacgtaa aacgagtgct tttatatgtg aggaaggaga acgatgacgt cttcgatgct 1740

ctgatgctga aatcacccac ggtgaagggt ctgatggaag cgctgtctga gaagtatggg 1800

ctgccagtgg agaaaatcac aaagctttat aagaagagca aaaagggcat cctggtcaac 1860

atggatgaca acatcattga gcactattca aatgaggaca ccttcatcct caacatggag 1920

agcatggtgg aaggcttcaa gatcacgctg atggagatct gagccctggg tgtcccctcg 1980

ataggagctt ttggtatact ccttcctggg agagatggga tctctgccgc cccaggacct 2040

ggagacccac ccatctcact cacctctcaa gactgttaca agactgctgg gaaggggggc 2100

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aagcctgagc ccctcagcaa atttcttctc gtgcc 2195

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<212> PRT
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Asp Glu Ala Trp Lys Ser Tyr Leu Glu Asn Pro Leu Thr Ala Ala Thr
35 40 45

Lys Ala Met Met Ser Ile Asn Gly Asp Glu Asp Ser Ala Ala Ala Leu
50 55 60

Gly Leu Leu Tyr Asp Tyr Tyr Lys Val Pro Arg Asp Lys Arg Leu Leu
65 70 75 80

Ser Val Ser Lys Ala Ser Asp Ser Gln Glu Asp Gln Asp Lys Arg Asn
85 90 95

Cys Leu Gly Thr Ser Glu Ala Gln Ile Asn Leu Ser Gly Gly Glu Asn
100 105 110

Arg Val Gln Val Leu Lys Thr Val Pro Val Asn Leu Cys Leu Ser Gln
115 120 125

Asp His Met Glu Asn Ser Lys Arg Glu Gln Tyr Ser Val Ser Ile Thr
130 135 140

Glu Ser Ser Ala Val Ile Pro Val Ser Gly Ile Thr Val Val Lys Ala
145 150 155 160

Glu Asp Phe Thr Pro Val Phe Met Ala Pro Pro Val His Tyr Pro Arg
165 170 175

Ala Asp Ser Glu Glu Gln Arg Val Val Ile Phe Glu Gln Thr Gln Tyr
180 185 190

Asp Leu Pro Ser Ile Ala Ser His Ser Ser Tyr Leu Lys Asp Asp Gln
195 200 205

Arg Ser Thr Pro Asp Ser Thr Tyr Ser Glu Ser Phe Lys Asp Gly Ala
210 215 220

Ser Glu Lys Phe Arg Ser Thr Ser Val Gly Ala Asp Glu Tyr Thr Tyr
225 230 235 240

Asp Gln Thr Gly Ser Gly Thr Phe Gln Tyr Thr Leu Glu Ala Thr Lys
245 250 255

Ser Leu Arg Gln Lys Gln Gly Glu Gly Pro Met Thr Tyr Leu Asn Lys
260 265 270

Gly Gln Phe Tyr Ala Ile Thr Leu Ser Glu Thr Gly Asp Asn Lys Cys
275 280 285

Phe Arg His Pro Ile Ser Lys Val Arg Ser Val Val Met Val Val Phe
290 295 300

Ser Glu Asp Lys Asn Arg Asp Glu Gln Leu Lys Tyr Trp Lys Tyr Trp
305 310 315 320

His Ser Arg Gln His Thr Ala Lys Gln Arg Val Leu Asp Ile Ala Asp
325 330 335

Tyr Lys Glu Ser Phe Asn Thr Ile Gly Asn Ile Glu Glu Ile Ala Tyr
340 345 350

Asn Ala Val Ser Phe Thr Trp Asp Val Asn Glu Glu Ala Lys Ile Phe
355 360 365

Ile Thr Val Asn Cys Leu Ser Thr Asp Phe Ser Ser Gln Lys Gly Val
370 375 380

Lys Gly Leu Pro Leu Met Ile Gln Ile Asp Thr Tyr Ser Tyr Asn Asn
385 390 395 400

Arg Ser Asn Lys Pro Ile His Arg Ala Tyr Cys Gln Ile Lys Val Phe
405 410 415

Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu Glu Arg Lys Gln
420 425 430

Asn Arg Lys Lys Gly Lys Gly Gln Ala Ser Gln Ala Gln Cys Asn Asn
435 440 445

Ser Ser Asp Gly Lys Met Ala Ala Ile Pro Leu Gln Lys Lys Ser Asp
450 455 460

Ile Thr Tyr Phe Lys Thr Met Pro Asp Leu His Ser Gln Pro Val Leu
465 470 475 480

Phe Ile Pro Asp Val His Phe Ala Asn Leu Gln Arg Thr Gly Gln Val
485 490 495

Tyr Tyr Asn Thr Asp Asp Glu Arg Glu Gly Ser Ser Val Leu Val Lys
500 505 510

Arg Met Phe Arg Pro Met Glu Glu Glu Phe Gly Pro Thr Pro Ser Lys
515 520 525

Gln Ile Lys Glu Glu Asn Val Lys Arg Val Leu Leu Tyr Val Arg Lys

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    530                 535                 540

Glu Asn Asp Asp Val Phe Asp Ala Leu Met Leu Lys Ser Pro Thr Val
545                 550                 555                 560

Lys Gly Leu Met Glu Ala Leu Ser Glu Lys Tyr Gly Leu Pro Val Glu
                565                 570                 575

Lys Ile Thr Lys Leu Tyr Lys Lys Ser Lys Lys Gly Ile Leu Val Asn
            580                 585                 590

Met Asp Asp Asn Ile Ile Glu His Tyr Ser Asn Glu Asp Thr Phe Ile
        595                 600                 605

Leu Asn Met Glu Ser Met Val Glu Gly Phe Lys Ile Thr Leu Met Glu
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Ile
625
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<211> 2831
<212> DNA
<213> murine

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<223> n = any nucleotide

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gaggagaatt aagagacgag tggtcagcag cgcctgcgag ccaaccagag acggatcgct     180

ggaacctcgg agaaggaag atg tcg aat gaa ctt gat ttc agg tct gtg cgg       232
                       Met Ser Asn Glu Leu Asp Phe Arg Ser Val Arg
                       1               5                  10

ttg ctg aag aat gac cct gtg agc ttc cag aag ttt ccc tac agt aat       280
Leu Leu Lys Asn Asp Pro Val Ser Phe Gln Lys Phe Pro Tyr Ser Asn
            15                  20                  25

gag gac gag gcc tgg aag aca tac ctg gag aac cct ttg acg gct gcc       328
Glu Asp Glu Ala Trp Lys Thr Tyr Leu Glu Asn Pro Leu Thr Ala Ala
        30                  35                  40

acc aaa gcc atg atg aga gtc aac ggg gac gag gag agt gtg gct gct       376
Thr Lys Ala Met Met Arg Val Asn Gly Asp Glu Glu Ser Val Ala Ala
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45 50 55

ctg agc ttc ctc tac gac tac tat atg ggt ccc aag gag aag cgg ata 424
Leu Ser Phe Leu Tyr Asp Tyr Tyr Met Gly Pro Lys Glu Lys Arg Ile
60 65 70 75

ctg tcc tcc agc act ggt ggc cgg aat gac caa gga aag aag ttc tac 472
Leu Ser Ser Ser Thr Gly Gly Arg Asn Asp Gln Gly Lys Lys Phe Tyr
80 85 90

cac agc atg gac tat gag ccg gat ctt gcc ccc ctc gag agc ccc aca 520
His Ser Met Asp Tyr Glu Pro Asp Leu Ala Pro Leu Glu Ser Pro Thr
95 100 105

cac ctc atg aaa ttt ttg aca gag aac gtg tct gga agt cca gac tac 568
His Leu Met Lys Phe Leu Thr Glu Asn Val Ser Gly Ser Pro Asp Tyr
110 115 120

aca gac cag ctc aag aaa aac aat ctg cta ggc ttg gag ggg gtt cta 616
Thr Asp Gln Leu Lys Lys Asn Asn Leu Leu Gly Leu Glu Gly Val Leu
125 130 135

ccc acc ccc ggc aag acc aat acc gtc ccc cca ggt ccg agt aaa ctg 664
Pro Thr Pro Gly Lys Thr Asn Thr Val Pro Pro Gly Pro Ser Lys Leu
140 145 150 155

gaa gcc agc tcc atg gac agc tac ctc ttg ccc gcc agt gac ata tat 712
Glu Ala Ser Ser Met Asp Ser Tyr Leu Leu Pro Ala Ser Asp Ile Tyr
160 165 170

gac aat ggc tcc ctc aac tca tta ttt gag agc att cat ggg gtt cca 760
Asp Asn Gly Ser Leu Asn Ser Leu Phe Glu Ser Ile His Gly Val Pro
175 180 185

ccc aca cag cgc tgg cag cca gac agc acc ttc aaa gat gac cca cag 808
Pro Thr Gln Arg Trp Gln Pro Asp Ser Thr Phe Lys Asp Asp Pro Gln
190 195 200

gag tct ctg ctc ttc cct gat att ctg aag aca tcc ccg gac ccc cca 856
Glu Ser Leu Leu Phe Pro Asp Ile Leu Lys Thr Ser Pro Asp Pro Pro
205 210 215

tgc cca gag gat tat cca ggc ctc aag agt gac ttt gaa tac acc ctg 904
Cys Pro Glu Asp Tyr Pro Gly Leu Lys Ser Asp Phe Glu Tyr Thr Leu
220 225 230 235

ggc tcc ccc aaa gcc att cac atc aaa gca ggg gag tca ccc atg gcc 952
Gly Ser Pro Lys Ala Ile His Ile Lys Ala Gly Glu Ser Pro Met Ala
240 245 250

tac ctc aac aag ggt cag ttc tac ccc gtc acc cta cgc acc cca gca 1000
Tyr Leu Asn Lys Gly Gln Phe Tyr Pro Val Thr Leu Arg Thr Pro Ala
255 260 265

gga ggg aaa ggc ctc gct ctg tcc tcc agc aaa gtc aag agc gtg gtg 1048
Gly Gly Lys Gly Leu Ala Leu Ser Ser Ser Lys Val Lys Ser Val Val

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      270                 275                 280

atg gtc gtg ttc gat aat gac aag gtc ccc gtg gag cag ctg cgt ttc      1096
Met Val Val Phe Asp Asn Asp Lys Val Pro Val Glu Gln Leu Arg Phe
    285                 290                 295

tgg agg cac tgg cat tcc cgg cag ccc acc gcc aag cag cgc gtc atc      1144
Trp Arg His Trp His Ser Arg Gln Pro Thr Ala Lys Gln Arg Val Ile
300                 305                 310                 315

gac gta gct gac tgt aag gaa aac ttc aac acg gtc cag cac att gaa      1192
Asp Val Ala Asp Cys Lys Glu Asn Phe Asn Thr Val Gln His Ile Glu
                320                 325                 330

gag gtg gcc tat aac gcg ctg tcc ttt gtg tgg aat gtc aac gag gaa      1240
Glu Val Ala Tyr Asn Ala Leu Ser Phe Val Trp Asn Val Asn Glu Glu
            335                 340                 345

gcc aag gtg ttt atc ggt gtc aac tgt ctg agc aca gac ttc tcc tcg      1288
Ala Lys Val Phe Ile Gly Val Asn Cys Leu Ser Thr Asp Phe Ser Ser
        350                 355                 360

cag aag gga gtg aag ggt gtc ccc ctg aac ttg caa att gac acc tat      1336
Gln Lys Gly Val Lys Gly Val Pro Leu Asn Leu Gln Ile Asp Thr Tyr
    365                 370                 375

gac tgt gga gca ggc act gag cgc ctg gta cac cgt gct gtc tgc cag      1384
Asp Cys Gly Ala Gly Thr Glu Arg Leu Val His Arg Ala Val Cys Gln
380                 385                 390                 395

atc aag atc ttc tgt gat aag gga gct gag agg aag atg cgc gat gat      1432
Ile Lys Ile Phe Cys Asp Lys Gly Ala Glu Arg Lys Met Arg Asp Asp
                400                 405                 410

gaa cgg aag cag ttt cga agg aag gtc aag tgc cca gac tcc agt aac      1480
Glu Arg Lys Gln Phe Arg Arg Lys Val Lys Cys Pro Asp Ser Ser Asn
            415                 420                 425

aat gca gga atc aag ggc tgc ctg ctg tca ggc ttc agg ggc aat gag      1528
Asn Ala Gly Ile Lys Gly Cys Leu Leu Ser Gly Phe Arg Gly Asn Glu
        430                 435                 440

acc aca tac ttg cgg cca gaa act gac ctg gag acc cag cct gtg ttg      1576
Thr Thr Tyr Leu Arg Pro Glu Thr Asp Leu Glu Thr Gln Pro Val Leu
    445                 450                 455

ttt atc ccc aat ctg cat ttt tcc agc cta cag cgc cca gga ggg gtt      1624
Phe Ile Pro Asn Leu His Phe Ser Ser Leu Gln Arg Pro Gly Gly Val
460                 465                 470                 475

gtc ccc tca gca gga cac agc agc tct gac agg ctg cct ctg aag cga      1672
Val Pro Ser Ala Gly His Ser Ser Ser Asp Arg Leu Pro Leu Lys Arg
                480                 485                 490

acc tgc tca ccc ttt gct gag gag ttt gag cct ctt cct tct aaa caa      1720
Thr Cys Ser Pro Phe Ala Glu Glu Phe Glu Pro Leu Pro Ser Lys Gln
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            495                 500                 505

gcc aag gaa gat gac ctt cag aga gtt ctg ttg tat gtg agg agg gag     1768
Ala Lys Glu Asp Asp Leu Gln Arg Val Leu Leu Tyr Val Arg Arg Glu
        510                 515                 520

aca gag gag gtg ttt gac gcg ctc atg ttg aag acc ccg gac ctg aag     1816
Thr Glu Glu Val Phe Asp Ala Leu Met Leu Lys Thr Pro Asp Leu Lys
    525                 530                 535

ggc ctg agg aat gcg atc tct gag aag tac ggc ctc ccc gag gag aat     1864
Gly Leu Arg Asn Ala Ile Ser Glu Lys Tyr Gly Leu Pro Glu Glu Asn
540                 545                 550                 555

att tgc aaa gtc tac aag aaa tgc aag cga ggc atc ctg gtt aac atg     1912
Ile Cys Lys Val Tyr Lys Lys Cys Lys Arg Gly Ile Leu Val Asn Met
                560                 565                 570

gac aac aac atc atc caa cac tac agc aac cac gtg gcc ttc ctg ctg     1960
Asp Asn Asn Ile Ile Gln His Tyr Ser Asn His Val Ala Phe Leu Leu
            575                 580                 585

gac atg ggt gag ctg gac ggc aag atc cag atc atc ctg aag gag cta     2008
Asp Met Gly Glu Leu Asp Gly Lys Ile Gln Ile Ile Leu Lys Glu Leu
        590                 595                 600

tgagggcccg gcctcaagcg tcccacaccc ggggcccggc tcaagccacg tacaacctct   2068

tctgtgtcag ctgttacttg aaatgccttt ctttgggaaa gaggtctcgc aagcaaccaa   2128

ctcggtgatg tccaagccag ggagagacca agaaggttcc aggatctaaa tgtcccaccc   2188

aggctcgaac tcactccaga gcttcctgaa agcacccagc ccaccggaga gtctgagcaa   2248

cacagaccca actgcctgct ttctcttcta agtcccgctg cagaggccct tacaggggac   2308

gggggtcaca ccaccttctc tgcagggcta cacccgctgt ctcgatcggt tctgacgttc   2368

actgtttcct ttctaccaac ttcagaccag agagttctca cactttggcc aaataacttg   2428

aaaactcgtg actttcacag cagatgcctt tgtgaggccc ttggagagga aactttctta   2488

ttgacttcct cggcacaaga tgtaagtcac catcatcgag ctgacaggaa caaataccct   2548

tgccacctac tgttgtacac atttcttatt tacagttttc attatgtgat tatatatata   2608

tatatgtaag tatatattat gtacatatat gcaacatttt gtatgtccat gttacatttt   2668

tatcatttca aaaatatgta tttcatattt cttgaactat ttttttagct gttattcgat   2728

tatgcatttt gtatatcata gggtttagta ataaaagcct acccatgcac acttaaaaaa   2788

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<212> PRT
<213> murine

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<223> n = any nucleotide

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Lys Thr Tyr Leu Glu Asn Pro Leu Thr Ala Ala Thr Lys Ala Met Met
        35                  40                  45

Arg Val Asn Gly Asp Glu Glu Ser Val Ala Ala Leu Ser Phe Leu Tyr
    50                  55                  60

Asp Tyr Tyr Met Gly Pro Lys Glu Lys Arg Ile Leu Ser Ser Ser Thr
65                  70                  75                  80

Gly Gly Arg Asn Asp Gln Gly Lys Lys Phe Tyr His Ser Met Asp Tyr
                85                  90                  95

Glu Pro Asp Leu Ala Pro Leu Glu Ser Pro Thr His Leu Met Lys Phe
            100                 105                 110

Leu Thr Glu Asn Val Ser Gly Ser Pro Asp Tyr Thr Asp Gln Leu Lys
        115                 120                 125

Lys Asn Asn Leu Leu Gly Leu Glu Gly Val Leu Pro Thr Pro Gly Lys
    130                 135                 140

Thr Asn Thr Val Pro Pro Gly Pro Ser Lys Leu Glu Ala Ser Ser Met
145                 150                 155                 160

Asp Ser Tyr Leu Leu Pro Ala Ser Asp Ile Tyr Asp Asn Gly Ser Leu
                165                 170                 175

Asn Ser Leu Phe Glu Ser Ile His Gly Val Pro Pro Thr Gln Arg Trp
            180                 185                 190

Gln Pro Asp Ser Thr Phe Lys Asp Asp Pro Gln Glu Ser Leu Leu Phe
        195                 200                 205

Pro Asp Ile Leu Lys Thr Ser Pro Asp Pro Pro Cys Pro Glu Asp Tyr
    210                 215                 220

Pro Gly Leu Lys Ser Asp Phe Glu Tyr Thr Leu Gly Ser Pro Lys Ala
225                 230                 235                 240

Ile His Ile Lys Ala Gly Glu Ser Pro Met Ala Tyr Leu Asn Lys Gly
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                245                 250                 255

Gln Phe Tyr Pro Val Thr Leu Arg Thr Pro Ala Gly Gly Lys Gly Leu
            260                 265                 270

Ala Leu Ser Ser Ser Lys Val Lys Ser Val Val Met Val Val Phe Asp
        275                 280                 285

Asn Asp Lys Val Pro Val Glu Gln Leu Arg Phe Trp Arg His Trp His
    290                 295                 300

Ser Arg Gln Pro Thr Ala Lys Gln Arg Val Ile Asp Val Ala Asp Cys
305                 310                 315                 320

Lys Glu Asn Phe Asn Thr Val Gln His Ile Glu Glu Val Ala Tyr Asn
                325                 330                 335

Ala Leu Ser Phe Val Trp Asn Val Asn Glu Glu Ala Lys Val Phe Ile
            340                 345                 350

Gly Val Asn Cys Leu Ser Thr Asp Phe Ser Ser Gln Lys Gly Val Lys
        355                 360                 365

Gly Val Pro Leu Asn Leu Gln Ile Asp Thr Tyr Asp Cys Gly Ala Gly
    370                 375                 380

Thr Glu Arg Leu Val His Arg Ala Val Cys Gln Ile Lys Ile Phe Cys
385                 390                 395                 400

Asp Lys Gly Ala Glu Arg Lys Met Arg Asp Asp Glu Arg Lys Gln Phe
                405                 410                 415

Arg Arg Lys Val Lys Cys Pro Asp Ser Ser Asn Asn Ala Gly Ile Lys
            420                 425                 430

Gly Cys Leu Leu Ser Gly Phe Arg Gly Asn Glu Thr Thr Tyr Leu Arg
        435                 440                 445

Pro Glu Thr Asp Leu Glu Thr Gln Pro Val Leu Phe Ile Pro Asn Leu
    450                 455                 460

His Phe Ser Ser Leu Gln Arg Pro Gly Gly Val Val Pro Ser Ala Gly
465                 470                 475                 480

His Ser Ser Ser Asp Arg Leu Pro Leu Lys Arg Thr Cys Ser Pro Phe
                485                 490                 495

Ala Glu Glu Phe Glu Pro Leu Pro Ser Lys Gln Ala Lys Glu Asp Asp
            500                 505                 510

Leu Gln Arg Val Leu Leu Tyr Val Arg Arg Glu Thr Glu Glu Val Phe
        515                 520                 525

Asp Ala Leu Met Leu Lys Thr Pro Asp Leu Lys Gly Leu Arg Asn Ala
    530                 535                 540
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Ile Ser Glu Lys Tyr Gly Leu Pro Glu Glu Asn Ile Cys Lys Val Tyr
545 550 555 560

Lys Lys Cys Lys Arg Gly Ile Leu Val Asn Met Asp Asn Asn Ile Ile
565 570 575

Gln His Tyr Ser Asn His Val Ala Phe Leu Leu Asp Met Gly Glu Leu
580 585 590

Asp Gly Lys Ile Gln Ile Ile Leu Lys Glu Leu
595 600

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<211> 4840
<212> DNA
<213> Drosophila

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gcagcaacat caaatgttag gccaaaatgc acaaaccgcc agcaacaaag gcagcaccaa 180

gcgaacgaaa caacaacagc tccacatacc acaaagagtg gcacattaga agcggccaaa 240

agcagccagc cgagagcatt gtgtaagcca aaggcccaga gagccaggct aaaagccccc 300

agacgcacaa caacaacaac aacaactaaa acagcacaaa gagtggcgaa aggtgcaccc 360

accagcaaaa cagcaacaac ggagcaacca acaacagcag cagcagcagc agcagccaca 420

tttcagttac agctccagac tcccaggttg cagactccca aagcaaacag actccagtcc 480

acgatccagc tccagttcca ccgatccgat ccactgctcc agcgtgctcg agtgccatag 540

atcctcacca agtgccaaaa tccgcatcct gatcccaaga gctcaaggca ccccggccca 600

aaattgagct gagaacgaaa cgaaggaagt tccttagtgc catagaaagc agttaatgaa 660

acaacgacta agacgaagat cgaccatcca gaaccggagg gagctaattg cgaacgaaag 720

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Pro His Leu Thr Val Pro Gln Lys Leu Asp Pro Asp Leu Tyr Gln Ala
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Asp Lys His Ile Asp Leu Ile Tyr Asn Asp Gly Ser Lys Thr Val Ile
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Thr Thr Ser Leu Val Asp Thr Ser Thr Asn Gly Ser Thr Arg Ser Arg
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Gln His Thr His Ser Arg Leu Gly Val Gly Val Gly Val Gly Ile Leu
35 40 45

Ser Asp Ala Ser Leu Ser Pro Ile Gln Gln Gly Ser Gly Gly His Ser
50 55 60

Gly Gly Gly Asn Thr Asn Ser Ser Pro Leu Ala Pro Asn Gly Val Pro
65 70 75 80

Leu Leu Thr Thr Met His Arg Ser Pro Asp Ser Pro Gln Pro Glu Leu
85 90 95

Ala Thr Met Thr Asn Val Asn Val Leu Asp Leu His Thr Asp Asn Ser
100 105 110

Lys Leu Tyr Asp Lys Glu Ala Val Phe Ile Tyr Glu Thr Pro Lys Val
115 120 125

Val Met Pro Ala Asp Gly Gly Gly Gly Asn Asn Ser Asp Glu Gly His
130 135 140

Ala Ile Asp Ala Arg Ile Ala Ala Gln Met Gly Asn Gln Ala Gln Gln
145 150 155 160

Gln Gln Gln Gln Gln Gln Gln Thr Glu His Gln Pro Leu Ala Lys Ile
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Glu Phe Asp Glu Asn Gln Ile Ile Arg Val Val Gly Pro Asn Gly Glu
180 185 190

Gln Gln Gln Ile Ile Ser Arg Glu Ile Ile Asn Gly Glu His His Ile
195 200 205

Leu Ser Arg Asn Glu Ala Gly Glu His Ile Leu Thr Arg Ile Val Ser
210 215 220

Asp Pro Ser Lys Leu Met Pro Asn Asp Asn Ala Val Ala Thr Ala Met
225 230 235 240

Tyr Asn Gln Ala Gln Lys Met Asn Asn Asp His Gly Gln Ala Val Tyr
245 250 255

Gln Thr Ser Pro Leu Pro Leu Asp Ala Ser Val Leu His Tyr Ser Gly
260 265 270

Gly Asn Asp Ser Asn Val Ile Lys Thr Glu Ala Asp Ile Tyr Glu Asp
275 280 285

His Lys Lys His Ala Ala Ala Ala Ala Ala Ala Ala Ala Gly Gly Gly Ser

```
    290                 295                 300

Ile Ile Tyr Thr Thr Ser Asp Pro Asn Gly Val Asn Val Lys Gln Leu
305                 310                 315                 320

Pro His Leu Thr Val Pro Gln Lys Leu Asp Pro Asp Leu Tyr Gln Ala
                325                 330                 335

Asp Lys His Ile Asp Leu Ile Tyr Asn Asp Gly Ser Lys Thr Val Ile
            340                 345                 350

Tyr Ser Thr Thr Asp Gln Lys Ser Leu Glu Ile Tyr Ser Gly Gly Asp
        355                 360                 365

Ile Gly Ser Leu Val Ser Asp Gly Gln Val Val Val Gln Ala Gly Leu
    370                 375                 380

Pro Tyr Ala Thr Thr Thr Gly Ala Gly Gly Gln Pro Val Tyr Ile Val
385                 390                 395                 400

Ala Asp Gly Ala Leu Pro Ala Gly Val Glu Glu His Leu Gln Ser Gly
                405                 410                 415

Lys Leu Asn Gly Gln Thr Thr Pro Ile Asp Val Ser Gly Leu Ser Gln
            420                 425                 430

Asn Glu Ile Gln Gly Phe Leu Leu Gly Ser His Pro Ser Ser Ser Ala
        435                 440                 445

Thr Val Ser Thr Thr Gly Val Val Ser Thr Thr Thr Ile Ser His His
    450                 455                 460

Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
465                 470                 475                 480

Gln His Gln Gln Gln Gln Gln His Pro Gly Asp Ile Val Ser Ala Ala
                485                 490                 495

Gly Val Gly Ser Thr Gly Ser Ile Val Ser Ser Ala Ala Gln Gln Gln
            500                 505                 510

Gln Gln Gln Gln Leu Ile Ser Ile Lys Arg Glu Pro Glu Asp Leu Arg
        515                 520                 525

Lys Asp Pro Lys Asn Gly Asn Ile Ala Gly Ala Ala Thr Ala Asn Gly
    530                 535                 540

Pro Gly Ser Val Ile Thr Gln Lys Ser Phe Asp Tyr Thr Glu Leu Cys
545                 550                 555                 560

Gln Pro Gly Thr Leu Ile Asp Ala Asn Gly Ser Ile Pro Val Ser Val
                565                 570                 575

Asn Ser Ile Gln Gln Arg Thr Ala Val His Gly Ser Gln Asn Ser Pro
            580                 585                 590
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Thr Thr Ser Leu Val Asp Thr Ser Thr Asn Gly Ser Thr Arg Ser Arg
        595                 600                 605

Pro Trp His Asp Phe Gly Arg Gln Asn Asp Ala Asp Lys Ile Gln Ile
    610                 615                 620

Pro Lys Ile Phe Thr Asn Val Gly Phe Arg Tyr His Leu Glu Ser Pro
625                 630                 635                 640

Ile Ser Ser Ser Gln Arg Arg Glu Asp Asp Arg Ile Thr Tyr Ile Asn
                645                 650                 655

Lys Gly Gln Phe Tyr Gly Ile Thr Leu Glu Tyr Val His Asp Ala Glu
            660                 665                 670

Lys Pro Ile Lys Asn Thr Thr Val Lys Ser Val Ile Met Leu Met Phe
        675                 680                 685

Arg Glu Glu Lys Ser Pro Glu Asp Glu Ile Lys Ala Trp Gln Phe Trp
    690                 695                 700

His Ser Arg Gln His Ser Val Lys Gln Arg Ile Leu Asp Ala Asp Thr
705                 710                 715                 720

Lys Asn Ser Val Gly Leu Val Gly Cys Ile Glu Glu Val Ser His Asn
                725                 730                 735

Ala Ile Ala Val Tyr Trp Asn Pro Leu Glu Ser Ser Ala Lys Ile Asn
            740                 745                 750

Ile Ala Val Gln Cys Leu Ser Thr Asp Phe Ser Ser Gln Lys Gly Gly
        755                 760                 765

Leu Pro Leu His Val Gln Ile Asp Thr Phe Glu Asp Pro Arg Asp Thr
    770                 775                 780

Ala Val Phe His Arg Gly Tyr Cys Gln Ile Lys Val Phe Cys Asp Lys
785                 790                 795                 800

Gly Ala Glu Arg Lys Thr Arg Asp Glu Glu Arg Arg Ala Ala Lys Arg
                805                 810                 815

Lys Met Thr Ala Thr Gly Arg Lys Lys Leu Asp Glu Leu Tyr His Pro
            820                 825                 830

Val Thr Asp Arg Ser Glu Phe Tyr Gly Met Gln Asp Phe Ala Lys Pro
        835                 840                 845

Pro Val Leu Phe Ser Pro Ala Glu Asp Met Glu Lys Ser Phe Tyr Gly
    850                 855                 860

His Glu Thr Asp Ser Pro Asp Leu Lys Gly Ala Ser Pro Phe Leu Leu
865                 870                 875                 880

His Gly Gln Lys Val Ala Thr Pro Thr Leu Lys Phe His Asn His Phe
                885                 890                 895
```

Pro Pro Asp Met Gln Thr Asp Lys Lys Asp His Ile Leu Asp Gln Asn
900 905 910

Met Leu Thr Ser Thr Pro Leu Thr Asp Phe Gly Pro Pro Met Lys Arg
915 920 925

Gly Arg Met Thr Pro Pro Thr Ser Glu Arg Val Met Leu Tyr Val Arg
930 935 940

Gln Glu Asn Glu Glu Val Tyr Thr Pro Leu His Val Val Pro Pro Thr
945 950 955 960

Thr Ile Gly Leu Leu Asn Ala Ile Glu Asn Lys Tyr Lys Ile Ser Thr
965 970 975

Thr Ser Ile Asn Asn Ile Tyr Arg Thr Asn Lys Lys Gly Ile Thr Ala
980 985 990

Lys Ile Asp Asp Asp Met Ile Ser Phe Tyr Cys Asn Glu Asp Ile Phe
995 1000 1005

Leu Leu Glu Val Gln Gln Ile Glu Asp Asp Leu Tyr Asp Val Thr
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Leu Thr Glu Leu Pro Asn Gln
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Ser Leu Ser Gly His Ala His Gly His Gly His Ala His Gln Leu His
            20                  25                  30

Gln His Thr His Ser Arg Leu Gly Val Gly Val Gly Val Gly Ile Leu
        35                  40                  45

Ser Asp Ala Ser Leu Ser Pro Ile Gln Gln Gly Ser Gly Gly His Ser
    50                  55                  60

Gly Gly Gly Asn Thr Asn Ser Ser Pro Leu Ala Pro Asn Gly Val Pro
65                  70                  75                  80

Leu Leu Thr Thr Met His Arg Ser Pro Asp Ser Pro Gln Pro Glu Leu
                85                  90                  95

Ala Thr Met Thr Asn Val Asn Val Leu Asp Leu His Thr Asp Asn Ser
            100                 105                 110

Lys Leu Tyr Asp Lys Glu Ala Val Phe Ile Tyr Glu Thr Pro Lys Val
        115                 120                 125

Val Met Pro Ala Asp Gly Gly Gly Gly Asn Asn Ser Asp Glu Gly His
    130                 135                 140

Ala Ile Asp Ala Arg Ile Ala Ala Gln Met Gly Asn Gln Ala Gln Gln
145                 150                 155                 160

Gln Gln Gln Gln Gln Gln Gln Thr Glu His Gln Pro Leu Ala Lys Ile
                165                 170                 175

Glu Phe Asp Glu Asn Gln Ile Ile Arg Val Val Gly Pro Asn Gly Glu
            180                 185                 190

Gln Gln Gln Ile Ile Ser Arg Glu Ile Ile Asn Gly Glu His His Ile
        195                 200                 205

Leu Ser Arg Asn Glu Ala Gly Glu His Ile Leu Thr Arg Ile Val Ser
    210                 215                 220

Asp Pro Ser Lys Leu Met Pro Asn Asp Asn Ala Val Ala Thr Ala Met
225                 230                 235                 240

Tyr Asn Gln Ala Gln Lys Met Asn Asn Asp His Gly Gln Ala Val Tyr
                245                 250                 255

Gln Thr Ser Pro Leu Pro Leu Asp Ala Ser Val Leu His Tyr Ser Gly
            260                 265                 270
```

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Gly Asn Asp Ser Asn Val Ile Lys Thr Glu Ala Asp Ile Tyr Glu Asp
        275                 280                 285

His Lys Lys His Ala Ala Ala Ala Ala Ala Ala Ala Gly Gly Gly Ser
    290                 295                 300

Ile Ile Tyr Thr Thr Ser Asp Pro Asn Gly Val Asn Val Lys Gln Leu
305                 310                 315                 320

Pro His Leu Thr Val Pro Gln Lys Leu Asp Pro Asp Leu Tyr Gln Ala
                325                 330                 335

Asp Lys His Ile Asp Leu Ile Tyr Asn Asp Gly Ser Lys Thr Val Ile
            340                 345                 350

Tyr Ser Thr Thr Asp Gln Lys Ser Leu Glu Ile Tyr Ser Gly Gly Asp
        355                 360                 365

Ile Gly Ser Leu Val Ser Asp Gly Gln Val Val Val Gln Ala Gly Leu
    370                 375                 380

Pro Tyr Ala Thr Thr Thr Gly Ala Gly Gly Gln Pro Val Tyr Ile Val
385                 390                 395                 400

Ala Asp Gly Ala Leu Pro Ala Gly Val Glu Glu His Leu Gln Ser Gly
                405                 410                 415

Lys Leu Asn Gly Gln Thr Thr Pro Ile Asp Val Ser Gly Leu Ser Gln
            420                 425                 430

Asn Glu Ile Gln Gly Phe Leu Leu Gly Ser His Pro Ser Ser Ser Ala
        435                 440                 445

Thr Val Ser Thr Thr Gly Val Val Ser Thr Thr Thr Ile Ser His His
    450                 455                 460

Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
465                 470                 475                 480

Gln His Gln Gln Gln Gln Gln His Pro Gly Asp Ile Val Ser Ala Ala
                485                 490                 495

Gly Val Gly Ser Thr Gly Ser Ile Val Ser Ser Ala Ala Gln Gln Gln
            500                 505                 510

Gln Gln Gln Gln Leu Ile Ser Ile Lys Arg Glu Pro Glu Asp Leu Arg
        515                 520                 525

Lys Asp Pro Lys Asn Gly Asn Ile Ala Gly Ala Ala Thr Ala Asn Gly
    530                 535                 540

Pro Gly Ser Val Ile Thr Gln Lys Ile Leu His Val Asp Ala Pro Thr
545                 550                 555                 560

Ala Ser Glu Ala Asp Arg Pro Ser Thr Pro Ser Ser Ser Ile Asn Ser
```

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Thr Glu Asn Thr Glu Ser Asp Ser Gln Ser Val Ser Gly Ser Glu Ser
580 585 590

Gly Ser Pro Gly Ala Arg Thr Thr Ala Thr Leu Glu Met Tyr Ala Thr
595 600 605

Thr Gly Gly Thr Gln Ile Tyr Leu Gln Thr Ser His Pro Ser Thr Ala
610 615 620

Ser Gly Ala Gly Gly Gly Ala Gly Pro Ala Gly Ala Ala Gly Gly Gly
625 630 635 640

Gly Val Ser Met Gln Ala Gln Ser Pro Ser Pro Gly Pro Tyr Ile Thr
645 650 655

Ala Asn Asp Tyr Gly Met Tyr Thr Ala Ser Arg Leu Pro Pro Gly Pro
660 665 670

Pro Pro Thr Ser Thr Thr Thr Phe Ile Ala Glu Pro Ser Tyr Tyr Arg
675 680 685

Glu Tyr Phe Ala Pro Asp Gly Gln Gly Gly Tyr Val Pro Ala Ser Thr
690 695 700

Arg Ser Leu Tyr Gly Asp Val Asp Val Ser Val Ser Gln Pro Gly Gly
705 710 715 720

Val Val Thr Tyr Glu Gly Arg Phe Ala Gly Ser Val Pro Pro Pro Ala
725 730 735

Thr Thr Thr Val Leu Thr Ser Val His His His Gln Gln Gln Gln Gln
740 745 750

Gln Gln Gln Gln His Gln Gln Gln Gln Gln Gln Gln His His Gln
755 760 765

Gln Gln Gln His His Ser Gln Asp Gly Lys Ser Asn Gly Gly Ala Thr
770 775 780

Pro Leu Tyr Ala Lys Ala Ile Thr Ala Ala Gly Leu Thr Val Asp Leu
785 790 795 800

Pro Ser Pro Asp Ser Gly Ile Gly Thr Asp Ala Ile Thr Pro Arg Asp
805 810 815

Gln Thr Asn Ile Gln Gln Ser Phe Asp Tyr Thr Glu Leu Cys Gln Pro
820 825 830

Gly Thr Leu Ile Asp Ala Asn Gly Ser Ile Pro Val Ser Val Asn Ser
835 840 845

Ile Gln Gln Arg Thr Ala Val His Gly Ser Gln Asn Ser Pro Thr Thr
850 855 860

```
Ser Leu Val Asp Thr Ser Thr Asn Gly Ser Thr Arg Ser Arg Pro Trp
865                 870                 875                 880

His Asp Phe Gly Arg Gln Asn Asp Ala Asp Lys Ile Gln Ile Pro Lys
                885                 890                 895

Ile Phe Thr Asn Val Gly Phe Arg Tyr His Leu Glu Ser Pro Ile Ser
            900                 905                 910

Ser Ser Gln Arg Arg Glu Asp Asp Arg Ile Thr Tyr Ile Asn Lys Gly
        915                 920                 925

Gln Phe Tyr Gly Ile Thr Leu Glu Tyr Val His Asp Ala Glu Lys Pro
    930                 935                 940

Ile Lys Asn Thr Thr Val Lys Ser Val Ile Met Leu Met Phe Arg Glu
945                 950                 955                 960

Glu Lys Ser Pro Glu Asp Glu Ile Lys Ala Trp Gln Phe Trp His Ser
                965                 970                 975

Arg Gln His Ser Val Lys Gln Arg Ile Leu Asp Ala Asp Thr Lys Asn
            980                 985                 990

Ser Val Gly Leu Val Gly Cys Ile  Glu Glu Val Ser His  Asn Ala Ile
        995                 1000                1005

Ala Val  Tyr Trp Asn Pro Leu  Glu Ser Ser Ala Lys  Ile Asn Ile
    1010                1015                1020

Ala Val  Gln Cys Leu Ser Thr  Asp Phe Ser Ser Gln  Lys Gly Gly
    1025                1030                1035

Leu Pro  Leu His Val Gln Ile  Asp Thr Phe Glu Asp  Pro Arg Asp
    1040                1045                1050

Thr Ala  Val Phe His Arg Gly  Tyr Cys Gln Ile Lys  Val Phe Cys
    1055                1060                1065

Asp Lys  Gly Ala Glu Arg Lys  Thr Arg Asp Glu Glu  Arg Arg Ala
    1070                1075                1080

Ala Lys  Arg Lys Met Thr Ala  Thr Gly Arg Lys Lys  Leu Asp Glu
    1085                1090                1095

Leu Tyr  His Pro Val Thr Asp  Arg Ser Glu Phe Tyr  Gly Met Gln
    1100                1105                1110

Asp Phe  Ala Lys Pro Pro Val  Leu Phe Ser Pro Ala  Glu Asp Met
    1115                1120                1125

Glu Lys  Val Gly Gln Leu Gly  Ile Gly Ala Ala Thr  Gly Met Thr
    1130                1135                1140

Phe Asn  Pro Leu Ser Asn Gly  Asn Ser Asn Ser Asn  Ser His Ser
    1145                1150                1155
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Lys Gly Ala Ser Pro Phe Leu Leu His Gly Gln Lys Val Ala Thr
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Pro Thr Leu Lys Phe His Asn His Phe Pro Pro Asp Met Gln Thr
1190 1195 1200

Asp Lys Lys Asp His Ile Leu Asp Gln Asn Met Leu Thr Ser Thr
1205 1210 1215

Pro Leu Thr Asp Phe Gly Pro Pro Met Lys Arg Gly Arg Met Thr
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Pro Pro Thr Ser Glu Arg Val Met Leu Tyr Val Arg Gln Glu Asn
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Glu Glu Val Tyr Thr Pro Leu His Val Val Pro Pro Thr Thr Ile
1250 1255 1260

Gly Leu Leu Asn Ala Ile Glu Asn Lys Tyr Lys Ile Ser Thr Thr
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    50                  55                  60

Gly Gly Gly Asn Thr Asn Ser Ser Pro Leu Ala Pro Asn Gly Val Pro
65                  70                  75                  80

Leu Leu Thr Thr Met His Arg Ser Pro Asp Ser Pro Gln Pro Glu Leu
                85                  90                  95

Ala Thr Met Thr Asn Val Asn Val Leu Asp Leu His Thr Asp Asn Ser
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Lys Leu Tyr Asp Lys Glu Ala Val Phe Ile Tyr Glu Thr Pro Lys Val
        115                 120                 125

Val Met Pro Ala Asp Gly Gly Gly Gly Asn Asn Ser Asp Glu Gly His
    130                 135                 140

Ala Ile Asp Ala Arg Ile Ala Ala Gln Met Gly Asn Gln Ala Gln Gln
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Gln Gln Gln Gln Gln Gln Gln Thr Glu His Gln Pro Leu Ala Lys Ile
                165                 170                 175

Glu Phe Asp Glu Asn Gln Ile Ile Arg Val Val Gly Pro Asn Gly Glu
            180                 185                 190

Gln Gln Gln Ile Ile Ser Arg Glu Ile Ile Asn Gly Glu His His Ile
        195                 200                 205

Leu Ser Arg Asn Glu Ala Gly Glu His Ile Leu Thr Arg Ile Val Ser
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Asp Pro Ser Lys Leu Met Pro Asn Asp Asn Ala Val Ala Thr Ala Met
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Gln Thr Ser Pro Leu Pro Leu Asp Ala Ser Val Leu His Tyr Ser Gly
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Gly Asn Asp Ser Asn Val Ile Lys Thr Glu Ala Asp Ile Tyr Glu Asp
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His Lys Lys His Ala Ala Ala Ala Ala Ala Ala Ala Gly Gly Gly Ser
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Ile Ile Tyr Thr Thr Ser Asp Pro Asn Gly Val Asn Val Lys Gln Leu
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Pro His Leu Thr Val Pro Gln Lys Leu Asp Pro Asp Leu Tyr Gln Ala
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Asp Lys His Ile Asp Leu Ile Tyr Asn Asp Gly Ser Lys Thr Val Ile
            340                 345                 350

Tyr Ser Thr Thr Asp Gln Lys Ser Leu Glu Ile Tyr Ser Gly Gly Asp
        355                 360                 365

Ile Gly Ser Leu Val Ser Asp Gly Gln Val Val Val Gln Ala Gly Leu
    370                 375                 380

Pro Tyr Ala Thr Thr Thr Gly Ala Gly Gly Gln Pro Val Tyr Ile Val
385                 390                 395                 400

Ala Asp Gly Ala Leu Pro Ala Gly Val Glu Glu His Leu Gln Ser Gly
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            420                 425                 430

Asn Glu Ile Gln Gly Phe Leu Leu Gly Ser His Pro Ser Ser Ser Ala
        435                 440                 445

Thr Val Ser Thr Thr Gly Val Val Ser Thr Thr Thr Ile Ser His His
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465                 470                 475                 480

Gln His Gln Gln Gln Gln Gln His Pro Gly Asp Ile Val Ser Ala Ala
                485                 490                 495

Gly Val Gly Ser Thr Gly Ser Ile Val Ser Ser Ala Ala Gln Gln Gln
            500                 505                 510

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        515                 520                 525

Lys Asp Pro Lys Asn Gly Asn Ile Ala Gly Ala Ala Thr Ala Asn Gly
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Glu Tyr Phe Ala Pro Asp Gly Gln Gly Gly Tyr Val Pro Ala Ser Thr
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Val Val Thr Tyr Glu Gly Arg Phe Ala Gly Ser Val Pro Pro Pro Ala
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785 790 795 800

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Ser Leu Val Asp Thr Ser Thr Asn Gly Ser Thr Arg Ser Arg Pro Trp
865                 870                 875                 880

His Asp Phe Gly Arg Gln Asn Asp Ala Asp Lys Ile Gln Ile Pro Lys
                885                 890                 895

Ile Phe Thr Asn Val Gly Phe Arg Tyr His Leu Glu Ser Pro Ile Ser
            900                 905                 910

Ser Ser Gln Arg Arg Glu Asp Asp Arg Ile Thr Tyr Ile Asn Lys Gly
        915                 920                 925

Gln Phe Tyr Gly Ile Thr Leu Glu Tyr Val His Asp Ala Glu Lys Pro
    930                 935                 940

Ile Lys Asn Thr Thr Val Lys Ser Val Ile Met Leu Met Phe Arg Glu
945                 950                 955                 960

Glu Lys Ser Pro Glu Asp Glu Ile Lys Ala Trp Gln Phe Trp His Ser
                965                 970                 975

Arg Gln His Ser Val Lys Gln Arg Ile Leu Asp Ala Asp Thr Lys Asn
            980                 985                 990

Ser Val Gly Leu Val Gly Cys Ile  Glu Glu Val Ser His  Asn Ala Ile
        995                 1000                1005

Ala Val  Tyr Trp Asn Pro Leu  Glu Ser Ser Ala Lys  Ile Asn Ile
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Ala Val  Gln Cys Leu Ser Thr  Asp Phe Ser Ser Gln  Lys Gly Gly
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Leu Pro  Leu His Val Gln Ile  Asp Thr Phe Glu Asp  Pro Arg Asp
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Thr Ala  Val Phe His Arg Gly  Tyr Cys Gln Ile Lys  Val Phe Cys
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Asp Lys  Gly Ala Glu Arg Lys  Thr Arg Asp Glu Glu  Arg Arg Ala
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Ser Leu Gln Ser Phe Tyr Gly His Glu Thr Asp Ser Pro Asp Leu
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Ser Ile Asn Asn Ile Tyr Arg Thr Asn Lys Lys Gly Ile Thr Ala

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Thr Leu  Thr Glu Leu Pro Asn  Gln
    1325                1330
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DATED this twenty-second day of August 2002.

Melbourne Health

by DAVIES COLLISION CAVE

Patent Attorneys for the Applicant

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